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Structures of the Intermediate Complexes in Friedel-Crafts Acylations

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Addition compounds of Lewis acids MX_n and acyl halides R—COX occur as intermediates in Friedel-Crafts acylations. IR and NMR studies on these intermediates have indicated the probable existence of structural isomers. In X-ray structural analysis, it is possible to distinguish two forms, *i.e.* the molecular form, in which the compounds are present as donor-acceptor complexes $R—CXO \rightarrow MX_n$, and the ionic form, in which they can be formulated as oxocarbenium salts $[R—CO]^+[MX_{n+1}]^-$. The compounds of the donor-acceptor type $R—CXO \rightarrow MX_n$ are characterized by the formation of a coordinate oxygen-metal bond; the transfer of electrons from the oxygen to the metal of the acceptor is always due to a weak donor-acceptor interaction. The positive charge of the aryloxocarbenium ions is partly delocalized over the aromatic nucleus. The positive charge in alkyloxocarbenium ions, on the other hand, is essentially localized on the carbon atom of the carbonyl group, as is confirmed by electron density distribution calculations.

1. Introduction

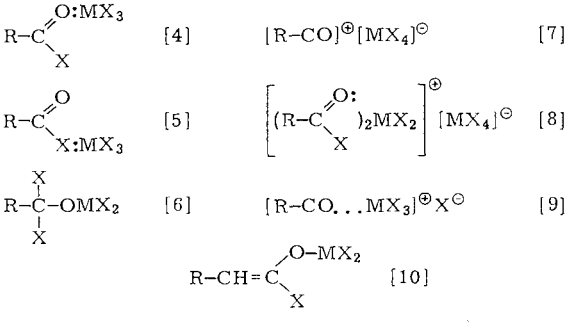
The Lewis acids MX_n ($n = 3,5$) can form more or less stable addition compounds with molecules that contain one or more nucleophilic atoms.

The complexes of the type $MX_n \cdot R—COX$ are formed in the course of Friedel-Crafts acylations

$$Ar—H + R—COX \xrightarrow{MX_n} Ar—CO—R + HX$$

from the catalyst MX_n and the acyl halide R—COX[1]. The role of these intermediates suggests two possible reaction mechanisms: one is a substitution mechanism[2], in which a donor-acceptor complex acts as the acylating agent, and the other is an ionic mechanism[3], in which the kinetics of the reaction are controlled by the formation of oxocarbenium ions $[R—CO]^+$.

Several formulas have been proposed for the structure of these intermediates (Scheme 1). Spectroscopic studies (IR, NMR) and X-ray structural analyses have now led to a clear picture of the nature and the geometry of these addition compounds.



Scheme 1. Views on the intermediates of Friedel-Crafts acylations.

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2. Spectroscopic Studies

2.1. IR Spectroscopy

IR spectroscopy has frequently been used during the past fifteen years for the study of the complexes of Lewis acids MX_n and acyl halides R—COX[11–25].

The vibrations of the carbonyl group lead to a strong band at about 1800 cm^{-1} in the spectra of the acyl halides R—COX. The most remarkable difference between the IR spectra of the acyl halides and their adducts $MX_n \cdot$R—COX is the displacement of this band. The *increase* in the frequency to 2200—2300 cm^{-1}, *i.e.* to the carbon-oxygen triple-bond range, is characteristic of the occurrence of oxocarbenium ions $[R—CO]^+$[11]; the *decrease* to 1550—1600 cm^{-1}, which is also observed when a ketone combines with a Lewis acid[26–28], is attributable to the formation of a coordinate bond between the oxygen atom and the metal atom of the electron acceptor: $R—CXO \rightarrow MX_n$.

Table 1 shows the characteristic vibration frequencies of selected complexes.

Table 1. IR spectra of selected solid complexes $MX_n \cdot$R—COX at room temperature (vs = very strong; s = strong; m = medium; w = weak; vw = very weak; sh = shoulder).

R—COX	MX_n	νCO [cm^{-1}] in R—COX	νCO [cm^{-1}] in $MX_n \cdot$R—COX		Ref.
CH_3COF	BF_3	1879 vs	1619 s	2299 vs	[11]
		1851 vs	1560 m	2220 m [a]	
	PF_5	1848 vs	1620 m	2297 vs	[12]
			1558 w		
	AsF_5	1848 vs	1620 w	2302 vs	[12]
			1558 w		
	SbF_5	1848 vs	1621 w	2294 vs	[12, 13]
			1554 w		
CH_3COCl	$AlCl_3$	1802 vs	1639 m	2305 vs	[14]
			1560 w	2200 sh [b]	
	$AlCl_3$	1808 vs	1637 vs	2307 s	[15]
			1567 s	2203 vs [c]	
	$GaCl_3$	—	1616 m	2300 s	[16]
			1540 w	2199 w [c]	
	$TiCl_4$	1802 vs	1760 vs	— [d]	[17]
			1620 s		
	$SbCl_5$	1800 vs	1709 m	2283 vs	[12]
			1587 w		
CH_3COBr	$AlBr_3$	1805 vs	1630 vs	2300 vs	[18]
			1555 vs		
C_2H_5COF	AsF_5	1845 vs	1608 m	2289 vs	[12]
	SbF_5	1845 vs	1610 m	2290 vs	[12]
C_2H_5COCl	$SbCl_5$	1828 vs	1790 sh	2232 vw	[12]
		1795 vs	1764 vs		
	$TiCl_4$	1840 vs	1650 s	—	[17]
		1780 vs			
$(CH_3)_2CHCOF$	SbF_5	1840 vs	1585 m	2270 vs	[19]
$(CH_3)_3CCOF$	SbF_5	1823 vs	1570 vs	2260 vs	[19]
n-C_3H_7COF	SbF_5	1824 vs	1610 m	2283 vs	[19]
			1545 w		
$(C_2H_5)_2CHCOF$	SbF_5	1837 vs	1578 m	2223 vs	[19]
$C_6H_5CH_2COF$	SbF_5	1843 vs	1599 m	2279 vs	[19]
			1516 m		
$(C_6H_5)_2CHCOF$	SbF_5	1847 vs	1578 vs	—	[19]
C_6H_5COF	AsF_5	1812 vs	1546 m	2228 vs	[12]
	SbF_5	1812 vs	1531 m	2212 vs	[12]
C_6H_5COCl	$AlCl_3$	1773 vs	1665 s	—	[20]
			1605 s		
			1585 s		
			1560 s		
	$TiCl_4$	1773 vs	1615 s	—	[21]
			1590 s		
			1573 s		
			1553 s		
	$SbCl_5$	1776 vs	1656 vs	2215 vw	[12]
		1736 vs	1575 vs		
C_6H_5COBr	$AlBr_3$	1763 s	1540 s	—	[21]
2-CH_3—C_6H_4COCl	$AlCl_3$	1770 vs	1602 s	2200 vs	[20]
			1585 s		
			1550 s		
			1525 s		
	$TiCl_4$	1770 vs	1602 s	—	[20]
			1580 s		
			1550 s		
			1505 s		
4-CH_3—C_6H_4COCl	$TiCl_4$	1768 s	1630 vs	—	[22]
	$SbCl_5$	1768 s	1550 vs	—	[22]
4-CH_3O—C_6H_4COCl	$TiCl_4$	1766 vs	1626 s	—	[22]
	$SbCl_5$	1766 vs	1546 w	2190 vs	[22]

Table 1. Continued

R—COX	MX_n	νCO [cm^{-1}] in R—COX	in MX_n·R—COX		Ref.
2,6-Xylyl-COCl	$AlCl_3$	1780 vs	1580 s 1560 m	2190 vs	[20]
	$TiCl_4$	1780 vs	1580 m 1560 w	2185 vs	[20]
Mesityl-COCl	$AlCl_3$	1785 vs	1596 s 1535 m	2190 vs	[14]
	$TiCl_4$	1785 vs	1590 m 1565 m	2170 vs	[21]
CH_2=CHCOF	SbF_5	1825	—	2250	[23]
CH_3CH=CHCOF	SbF_5	1815	—	2240	[23]
$(CH_3)_2C$=CHCOF	SbF_5	1800	—	2230	[23]
CH_2=$C(CH_3)$COF	SbF_5	1815	—	2240	[23]
CH_3CH=$C(CH_3)$COF	SbF_5	1800	—	2230	[23]
C_6H_5CH=CHCOF	SbF_5	1805	—	2210	[23]
FOC—$(CH_2)_2$—COF	SbF_5	1845 1792	1630 1550	2300	[24]
FOC—$(CH_2)_3$—COF	SbF_5	1842	—	2290	[24]
FOC—$(CH_2)_4$—COF	SbF_5	1840	—	2290	[24]
FOC—$(CH_2)_5$—COF	SbF_5	1836		2286	[24]
FOC—$(CH_2)_6$—COF	SbF_5	1836	—	2285	[24]
FOC—$(CH_2)_7$—COF	SbF_5	1837	—	2282	[24]
p-FOC—C_6H_4—COF	SbF_5	1812	—	2262	[24]
Cyclopropyl-COF	SbF_5	1815	—	2225	[25]
Cyclobutyl-COF	SbF_5	1825	—	2205	[25]
Cyclopentyl-COF	SbF_5	1830	—	2260	[25]
Cyclohexyl-COF	SbF_5	1835	—	2255	[25]
Cycloheptyl-COF	SbF_5	1825	—	2210	[25]
Cycloundecyl-COF	SbF_5	1840	—	2260	[25]
2-Norbornyl-COF	SbF_5	1840	—	2250	[25]
1-Adamantyl-COF	SbF_5	1835	—	2255	[25]
Cyclopropyl-COCl	$SbCl_5$	1780	—	2245	[25]
Cyclobutyl-COCl	$SbCl_5$	1800	—	2239	[25]
Cyclopentyl-COCl	$SbCl_5$	1790	—	2240	[25]
Cyclohexyl-COCl	$SbCl_5$	1800	—	2240	[25]
2-Norbornyl-COCl	$SbCl_5$	1800	—	2240	[25]

[a] At −40 C.
[b] At −15 C
[c] Liquid.
[d] At −20 C.

While IR spectroscopy is a great help in the classification of these complexes, it is not enough by itself to allow the definite assignment of the structure of an oxocarbenium salt or of a nonionic addition compound to the adduct. Bands at 2200—2300 cm^{-1} and at 1550 cm^{-1} very often occur together in the IR spectra (Table 1). *Cook*[15] found this situation in the investigation of mixtures of acetyl chloride and aluminum chloride, and assumed that a mixture of the ionic form and the molecular form is present. The idea that an equilibrium exists between the two forms has been generally accepted since that time. The position of this equilibrium

$$[R\text{–}CO]^{\oplus}[MX_{n+1}]^{\ominus} \rightleftharpoons R\text{–}C(=O\rightarrow MX_n)\text{–}X$$

depends on the complex under investigation as well as on the experimental conditions:

a) Acyl fluorides and metal fluorides give mainly ionic compounds[13, 23–25]. The affinity of the fluoride ion for the metal of the acceptor has been demonstrated by investigations on the protonation and dehydration of carboxylic acids by the mixtures BF_3/HF, SbF_5/HF and $SbF_5/SO_2/FSO_3H$[29–32]. The formation of stable anions BF_4^- or SbF_6^- in these reactions favors the displacement of the equilibrium toward the ionic form.

b) Dioxodicarbenium ions can be prepared from difluorides of dicarboxylic acids FOC—$(CH_2)_n$—COF only for $n \geq 3$. The dication cannot be formed from succinyl difluoride ($n=2$), since the distance between the charges is too small. Addition of the Lewis acid SbF_5 is reported to lead to the mixed addition compound $[SbF_5 \cdot FOC\text{—}(CH_2)_2\text{—}CO]^+[SbF_6]^-$[24].

c) 2,6-Dimethylbenzoyl chloride and mesitoyl chloride, unlike benzoyl chloride, form addition compounds having ionic character with the acceptors $AlCl_3$ and $TiCl_4$[14, 20, 21]. This could be due to intramolecular steric hindrance, since the bulky methyl groups could favor the formation of a $C\equiv O^+$ bond in the complex. The molecule would thus become planar again, with the result that a conjugated system could develop.

d) The equilibrium can be displaced toward the ionic form or toward the molecular form by the use of suitable solvent. *Cook*[15] showed that the adduct of acetyl chloride and aluminum chloride predominantly dissociates into ions in a solvent having a high dielectric constant such as nitrobenzene ($\varepsilon = 36.1$), whereas only the molecular form is present in a solvent such as chloroform ($\varepsilon = 5.05$).

The formation of oxocarbenium ions is generally characterized by a single strong absorption band in the carbon-oxygen triple-bond region (2200—2300 cm^{-1}); however, two bands have been found in this region for some compounds, one at 2200 cm^{-1} and the other at 2300 cm^{-1} (Table 1). In the investigation of the complex $AlCl_3 \cdot CH_3COCl$ in the solid state at −15 °C, *Susz* and *Wuhrmann*[14] attributed the strong vibration at the higher frequency to the particle $[CH_3CO]^+$ but gave no assignment for the weak shoulder at 2200 cm^{-1}.

Cook[15], who obtained this complex in the liquid state by mixing the two components in the absence of solvent, found two strong bands at 2307 cm^{-1} and 2203 cm^{-1} and a very strong band at 1637 cm^{-1}. This last band was assigned by the author to the molecular compound, and the absorption at 2307 cm^{-1} to the free acetylium ion $[CH_3CO]^+$. *Cook* expresses the opinion that the band at 2203 cm^{-1} is due either to the complex ion $[CH_3CO \ldots AlCl_3]^+$ proposed by *Dilthey*[9] or again to an association of the acetylium and tetrachloroaluminate ions $[CH_3—\overset{+}{C}=O][Cl—AlCl_3]^-$.

In a later publication on the complex $GaCl_3 \cdot CH_3COCl$[16], *Cook* reversed the earlier assignment and attributed the band at 2200 cm^{-1} to the free acetylium ion and that at 2300 cm^{-1} to the complex ion $[CH_3CO \ldots AlCl_3]^+$. *Cook* deduced this new hypothesis from the analogy with the complexes $MX_n \cdot CH_3CN$ where the frequency of the C—N stretching vibration is higher in the complex than in the free nitrile[33–35].

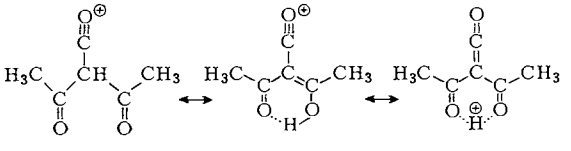
Gates and *Steele*[36], on the other hand, on the basis of an IR and Raman study of the addition compound $SbCl_5 \cdot CH_3COCl$, reject the existence of a complex salt $[CH_3CO \ldots SbCl_5]^+Cl^-$ and assign the strong absorption at 2300 cm^{-1} to the carbonyl vibration of the free acetylium ion.

Cassimatis et al.[18,37] recently suggested the occurrence of two types of acetylium ion in the compounds $AlCl_3 \cdot CH_3COCl$ and $AlBr_3 \cdot CH_3COBr$. Type I, with a characteristic absorption at 2200 cm^{-1}, has the formula $CH_3—C\equiv O^+$, while type II, with the band at 2300 cm^{-1}, is a resonance hybrid between the three structures

$$CH_3—C\equiv\overset{\oplus}{O} \leftrightarrow CH_3—\overset{\oplus}{C}=O \leftrightarrow \overset{\oplus}{H}CH_2=C=O$$

with predominance of the hyperconjugated form.

Germain, Commeyras, and *Casadevall*[38] have isolated and characterized two crystalline tetrachloroaluminates. The one that causes the absorption at 2300 cm^{-1} contains the acetylium ion. The other, which absorbs strongly at 2200 cm^{-1}, contains the diacetylacetylium ion *(1)*, which is formed by reaction of the acetylium ion with acetyl chloride in a ratio of 1:2.



(1)

The contribution of the third resonance form, the ketene structure, is thought to be the cause of the decrease in the carbonyl frequency by about 100 cm^{-1} in relation to that of the acetylium ion. This effect also explains the frequency of 2190 cm^{-1} in the mesitoylium ion[14].

Mention should also be made of a publication by *Cassimatis* and *Susz*[17] on the adduct $TiCl_4 \cdot CH_3COCl$, which has no absorption in the CO triple-bond region. The authors assign the band at 1620 cm^{-1} to the carbonyl vibration, which is thought to be disturbed by the attachment of the acceptor $TiCl_4$ to the oxygen atom. They explain the occurrence of another strong absorption at 1760 cm^{-1} by the possibility of a dipole-dipole interaction[39], which could lead to a molecular compound $CH_3COCl \ldots TiCl_4$, or by the assumption of a weak dative bond between $TiCl_4$ and the chlorine atom of acetyl chloride, in which no ionization occurs. The authors rule out the existence of a compound of the type

$$CH_2=C(Cl)—O—AlCl_2$$

proposed by *Illari*[10]. While the value of 1620 cm^{-1} is acceptable for a CC double bond, 1760 cm^{-1} seems to them to be much too high for the frequency of a carbonyl vibration disturbed by a Lewis acid as strong as $TiCl_4$.

2.2. Nuclear Magnetic Resonance

Measurements of the nuclear magnetic resonance add to and extend the information provided by IR spectroscopy on the structure and behavior of the addition compounds under investigation in solution. The results are particularly informative, since it is in the dissolved state that these complexes function as intermediates in acylations.

Olah et al. have made extensive use of this technique[12,19,23–25,32,40] for the investigation of the fluoride adducts dissolved in liquid sulfur dioxide or in anhydrous hydrogen fluoride. The resolution of the ^1H-NMR spectra is as good as that of the ^{19}F- or ^{13}C-NMR spectra; they exhibit a characteristic shift of the signals due to the protons α to the carbonyl group toward lower fields.

Two types of signals appear, and these are assigned to two particles having different structures[12]. The species with $\delta \approx -4.1$ ppm is the oxocarbenium ion $[R—CO]^+$, whose positive charge reduces the shielding by the electrons and so causes a strong chemical shift. The smaller chemical shift ($\delta \approx -2.9$ ppm) in the other particle points to stronger shielding in the strongly polarized coordination compound *(2)*. The spectra generally contain both signals, and again show that the two species occur together in solution[12,19].

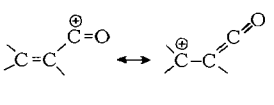
$$R—\overset{\delta\oplus}{\underset{X}{C}}O \rightarrow \overset{\delta\ominus}{M}X_n \qquad (2)$$

Nuclear magnetic resonance also provides further information on the structure of the oxocarbenium ions.

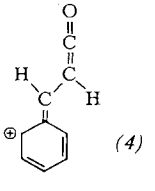
From the study of the ^1H and ^{13}C resonances for solutions of the complexes $[CH_3CO]^+[SbF_6]^-$, $[CD_3CO]^+[SbF_6]^-$, and $[CH_3{}^{13}CO]^+[SbF_6]^-$ in SO_2 or HF[19], it can be concluded that the positive charge of the acetylium ion is mainly localized on the carbon atom of the carbonyl group:

$$CH_3—\overset{+}{C}=O$$

In the alkenyloxocarbenium ions, the chemical shift of the protons β to the carbonyl group is greater than that of the protons in the α position. This points to a contribution by the resonance structures *(3)*, and particularly in the case



(3)



(4)

of the cinnamoylium ion to a high contribution by the limiting form *(4)*[23], in which delocalization of the positive charge over the aromatic ring is possible.

From the NMR spectra of the phenyloxocarbenium ion and some of its *o*-, *m*-, and *p*-substituted derivatives, *Olah* and *Westerman*[41] concluded that considerable delocalization of the charge over the aromatic ring is to be expected.

3. X-Ray Structural Investigations

Recent X-ray structural analyses yield a clear picture of the structure and stereochemistry of the addition compounds under investigation in the solid state. These studies show the presence of either molecular donor-acceptor complexes of the type $R{-}CXO{\rightarrow}MX_n$ or adducts $[R{-}CO]^+[MX_{n+1}]^-$ having an ionic structure. No other species were detectable in the crystalline state.

3.1. Donor-Acceptor Addition Compounds (Molecular Form)

The crystal structures of the following molecular addition compounds have now been determined:

acceptor $AlCl_3$, donor propionyl chloride[42], benzoyl chloride[43], *o*-, *m*-, and *p*-toluoyl chloride[44];

acceptor $SbCl_5$, donor 1/2 succinyl dichloride[45], benzoyl chloride[46], *m*-toluoyl chloride[46], and *p*-toluoyl chloride[47].

The bonding between the acyl halide and the Lewis acid is brought about in these adducts by the oxygen atom, which shares a lone pair of electrons with the metal of the electron acceptor.

The formation of the coordinate metal-oxygen bond leads to a tetrahedral environment for the aluminum atom and an octahedral environment for the antimony atom (Fig. 1). The coordination polyhedra $AlCl_3O$ and $SbCl_5O$ are highly distorted because of intramolecular steric hindrance. In the first instance, the dissimilarity of the atoms of the coordination polyhedron causes the chlorine atoms to be displaced toward the oxygen atom (van der Waals radii: O = 1.40, Cl = 1.80 Å). Furthermore, the proximity of the acyl chloride group leads to an interaction with the chlorine atoms of the polyhedron, as a result of which the chlorine-metal-oxygen bond angles become unequal[42, 44–47].

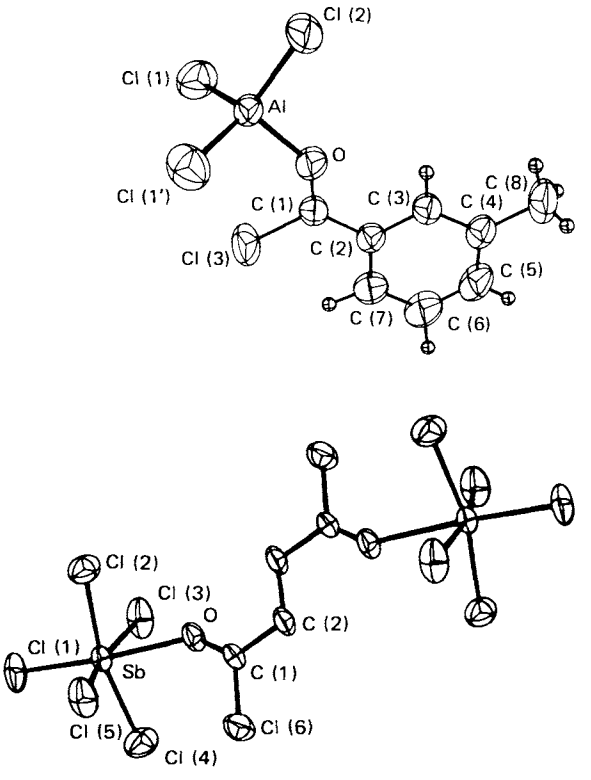


Fig. 1. Crystal structure of the molecular compounds $AlCl_3 \cdot 3\text{-}CH_3{-}C_6H_4COCl$ (top) and $2\,SbCl_5 \cdot ClOCCH_2CH_2COCl$ (bottom).

The deformation of the coordination polyhedra can be seen from Table 2, which shows the chlorine-metal-oxygen and chlorine-metal-chlorine bond angles. Comparison of these bond angles with those in compounds of hexacoordinate antimony $SbCl_5 \cdot POCl_3$, $SbCl_5 \cdot HCON(CH_3)_2$, and $SbCl_5 \cdot (CH_3)_3PO$[48, 49] shows particularly clearly that the displacement of the chlorine atom toward the oxygen atom increases with the length of the metal-oxygen bond.

The donor-acceptor interaction in these molecular addition compounds consists in the transfer of electrons from the oxygen of the acyl chloride to the metal of the Lewis acid. This transfer is limited, however, by the electron attraction of the chlorine atom in the acyl chloride, which is therefore only

Table 2. Length of the metal-oxygen bond and bond angles in the coordination polyhedra of the donor-acceptor complexes.

Compound	M—O [Å]	∢ M—O—C [ ]	mean ∢ [ ] [a] Cl—M—O	Cl—M—Cl*	Ref.
$AlCl_3 \cdot C_6H_5COCl$	1.819	141.7	105.2	113.3	[43]
$AlCl_3 \cdot 2\text{-}CH_3{-}C_6H_4COCl$	1.824	146.2	104.0	114.2	[44]
$AlCl_3 \cdot 4\text{-}CH_3{-}C_6H_4COCl$	1.828	144.6	104.9	113.6	[44]
$AlCl_3 \cdot 3\text{-}CH_3{-}C_6H_4COCl$	1.835	138.3	105.7	112.9	[44]
$AlCl_3 \cdot C_2H_5COCl$	1.847	141.6	105.1	113.4	[42]
$2SbCl_5 \cdot ClOCCH_2CH_2COCl$	2.428	143.6	82.9	97.1	[45]
$SbCl_5 \cdot C_6H_5COCl$	2.317	145.9	83.8	96.2	[46]
$SbCl_5 \cdot 3\text{-}CH_3{-}C_6H_4COCl$	2.295	144.7	84.0	96.0	[46]
$SbCl_5 \cdot 4\text{-}CH_3{-}C_6H_4COCl$	2.253	146.6	84.1	95.9	[47]
$SbCl_5 \cdot POCl_3$	2.17	—	85.3	94.7	[49]
$SbCl_5 \cdot HCON(CH_3)_2$	2.05	—	87.0	93.0	[48]
$SbCl_5 \cdot (CH_3)_3PO$	1.94	—	88.3	91.8	[49]

[a] Cl* denotes the chlorine atom situated opposite the oxygen atom in the $SbCl_5O$ coordination polyhedron.

a weak donor. The length of the coordinate bond Al—O between aluminum and oxygen is practically the same in all addition compounds of the Lewis acid $AlCl_3$, and is roughly the same as the bond length in inorganic compounds of tetracoordinate aluminum (1.80 Å)[50]. The antimony-oxygen bond Sb—O, on the other hand, varies over a wide range according to the nature of the donor (Table 2). The Sb—O distance of 2.253 Å in the compound $SbCl_5 \cdot 4\text{-}CH_3—C_6H_4COCl$ underlines the weak donor character of *p*-toluoyl chloride in comparison with trimethylphosphane oxide in the adduct $SbCl_5 \cdot (CH_3)_3PO$, in which the antimony-oxygen distance is only 1.94 Å[49]. In the compound $2SbCl_5 \cdot ClOCCH_2CH_2—COCl$, the extremely weak Sb—O bond with a length of 2.428 Å is due to the proximity of the two functional groups of the succinyl dichloride[45].

It must be emphasized that the M—O—C bond angle in all molecular addition compounds is much greater than the 120° that one would expect for sp^2 hybridization of the oxygen atom (Table 2). However, no correlation has been found between the size of this angle and the length of the metal-oxygen bond. This deviation of the angle has been ascribed to intramolecular steric hindrance or to the packing in the crystal[42, 44–47].

Finally, it should be noted that the lengths of the carbon-oxygen bonds are the same in all these addition compounds, as are the lengths of the carbon-chlorine bonds (Table 3).

Table 3. Lengths of the carbon-oxygen and carbon-chlorine bonds in the coordination polyhedra of the donor-acceptor complexes.

Compound	C—O [Å]	C—Cl [Å]	Ref.
$AlCl_3 \cdot C_2H_5COCl$	1.215(8)	1.709(9)	[42]
$AlCl_3 \cdot C_6H_5COCl$	1.226(8)	1.716(8)	[43]
$AlCl_3 \cdot 2\text{-}CH_3—C_6H_4COCl$	1.235(6)	1.721(4)	[44]
$AlCl_3 \cdot 3\text{-}CH_3—C_6H_4COCl$	1.232(5)	1.710(5)	[44]
$AlCl_3 \cdot 4\text{-}CH_3—C_6H_4COCl$	1.235(3)	1.712(1)	[44]
$2SbCl_5 \cdot ClOCCH_2CH_2COCl$	1.211(12)	1.713(11)	[45]
$SbCl_5 \cdot C_6H_5COCl$	1.236(7)	1.712(5)	[46]
$SbCl_5 \cdot 3\text{-}CH_3—C_6H_4COCl$	1.211(6)	1.710(4)	[46]
$SbCl_5 \cdot 4\text{-}CH_3—C_6H_4COCl$	1.220(11)	1.726(9)	[47]

To a first approximation, therefore, these bonds seem to be independent of the nature of the donor (the acyl chloride) and of the nature of the acceptor (the Lewis acid). In other words, the donor-acceptor interaction is evident only in the metal-oxygen bond, and this interaction is very weak.

3.2. Oxocarbenium Salts (Ionic Form)

In this type of addition compound, the ion X^- formed on ionization of the acyl chloride R—COX provides the electron pair to complete the electron complement in the metal of the acceptor.

These compounds are salts, in which the ions $[MX_{n+1}]^-$ and $[R—CO]^+$ can be detected. The cations $[R—CO]^+$ were originally named oxocarbonium ions, but since true carbonium ions containing pentacoordinate carbon have been found[50a], they should be referred to as oxocarbenium ions. As was shown by NMR studies, the positive charge of the ion $[CH_3CO]^+$ is essentially localized on the carbon atom of the carbonyl group. According to *Olah*[41], the most appropriate name is acylium ion, since this covers all three resonance forms of the cation $[R—CO]^+$:

$$R—C\equiv\overset{\oplus}{O} \leftrightarrow R—\overset{\oplus}{C}=O \leftrightarrow \overset{\oplus}{R}=C=O$$

The geometry of the following alkyloxocarbenium and aryloxocarbenium ions has been established by X-ray structural investigations: the methyloxocarbenium ion in the compounds $[CH_3CO]^+[SbF_6]^-$[51], $[CH_3CO]^+[SbCl_6]^-$[52], and $[CH_3CO]^+[AlCl_4]^-$[52], the ethyloxocarbenium ion in $[C_2H_5CO]^+[GaCl_4]^-$[53], the isopropyloxocarbenium ion in $[(CH_3)_2CHCO]^+[SbCl_6]^-$[53], the 2-tolyloxocarbenium ion in $[2\text{-}CH_3—C_6H_4CO]^+[SbCl_6]^-$[54], and the 4-tolyloxocarbenium ion in $[4\text{-}CH_3—C_6H_4CO]^+[SbCl_6]^-$[47].

It was shown by an X-ray crystallographic study that the complexes of antimony pentachloride and 2,6-dimethylbenzoyl

Table 4. Geometry of the oxocarbenium ions.

Cation	Anion	C(1)—O [Å]	C(1)—C(2) [Å]	∢O—C(1)—C(2) [°]	Ref.
$[CH_3CO]^+$	$[SbF_6]^-$	1.108(15)	1.385(16)	177.20(1.60)	[51]
	$[SbCl_6]^-$	1.109(30)	1.452(24)	180.00	[52]
	$[AlCl_4]^-$	[a]	[a]	179.79(0.54)	[52]
$[(C_2H_5CO]^+$	$[GaCl_4]^-$	1.099(20)	1.435(24)	177.45(1.35)	[53]
$[(CH_3)_2CHCO]^+$	$[SbCl_6]^-$	1.116(10)	1.439(12)	175.72(0.48)	[53]
$[2\text{-}CH_3—C_6H_4CO]^+$	$[SbCl_6]^-$	1.111(13)	1.387(14)	178.69(0.77)	[54]
$[4\text{-}CH_3—C_6H_4CO]^+$	$[SbCl_6]^-$	1.097(9)	1.396(10)	179.39(0.55)	[47]

[a] Owing to the random distribution of the $[CH_3CO]^+$ cations in the unit cell the individual C(1)—O and C(1)—C(2) distances cannot be determined from the X-ray data. However, the distance between the atoms O and C(2) (2.56 Å) approaches that in the salt $[CH_3CO]^+[SbCl_6]^-$: 1.109 + 1.452 = 2.561 Å.

chloride or mesitoyl chloride (2,4,6-trimethylbenzoyl chloride) in the solid state are oxocarbenium salts. However, it has not been possible to establish the precise geometry of the cations in these complexes, since the two ions are not oriented regularly in the unit cell[55].

The principal data on the structure of these oxocarbenium ions are shown in Table 4. We have used the following designations: C(1) for the carbon atom of the carbonyl group and C(2) for the carbon atom α to this group. Figure 2 shows the structure of the ionic compounds $[CH_3CO]^+[SbCl_6]^-$ and $[(CH_3)_2CHCO]^+[SbCl_6]^-$.

The average C(1)—C(2) bond length in the alkyloxocarbenium ion is 1.43 Å. One would expect a much greater distance between two carbon atoms where one is sp^3 hybridized and the other sp hybridized; for example, the CN bond in acetonitrile CH_3CN[57], which is isoelectronic with the acetylium ion $[CH_3CO]^+$, has a length of 1.458 Å. Comparable results have also been obtained for the C(1)—C(2) bond lengths in aryloxocarbenium ions. The bonds in the 2-tolyloxocarbenium and 4-tolyloxocarbenium ions [1.387(14) and 1.396(10) Å] are only slightly shorter than the distance between an sp^2 hybridized and an sp hybridized carbon atom in benzonitrile

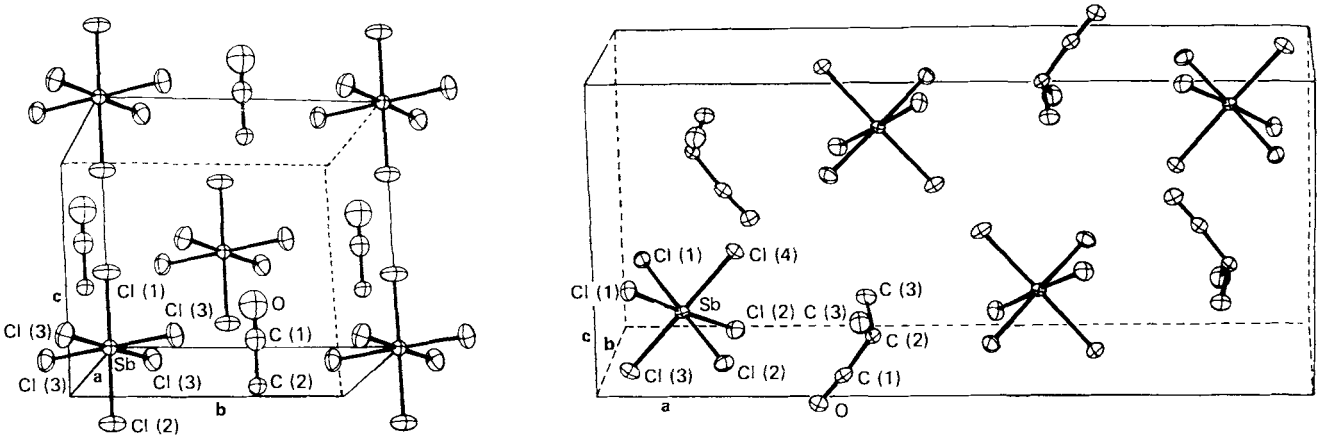


Fig. 2. Crystal structure of the ionic compounds $[CH_3CO]^+[SbCl_6]^-$ (left) and $[(CH_3)_2CHCO]^+[SbCl_6]^-$ (right).

The arrangement of the oxygen atom and the carbon atoms C(1) and C(2) is linear in all oxocarbenium ions. A slight deviation is found only in the isopropyloxocarbenium ion, where the angle O—C(1)—C(2) is 175.72(0.48)°; this is probably due to crystal lattice forces[53]. The packing in the crystal should also be such that the aryloxocarbenium ions are not strictly planar. It is in fact found that the oxygen atom and the carbon atom C(1) lie appreciably outside the central plane in the 2-tolyloxocarbenium and 4-tolyloxocarbenium ions[47,54].

An important point is the length of the carbon-oxygen bond, which is the same in all these oxocarbenium ions (Table 4). This bond thus appears to be independent of the residue R. The average bond length of 1.11 ± 0.01 Å is smaller than in most aldehydes or ketones, but similar to the bond length in carbon monoxide (1.128 Å). This points to a partial triple-bond character[56].

The structural analyses do not indicate any weakening of the C(1)—C(2) bond, which one should expect if the polarity of this bond was increased by the inductive effect of methyl groups on the carbon atom C(2). The C—C bond lengths, which were measured by *le Carpentier* and *Weiss*[52,53] in the methyl-, ethyl-, and isopropyloxocarbenium ions, do indeed agree within the limits of error. However, chemical findings point to weakening of this bond with increasing substitution on the carbon atom α to the carbonyl group. Thus the ion $[(CH_3)_2CHCO]^+$ is reported to be partly dissociated at room temperature, and the ion $[(CH_3)_3CCO]^+$ to be almost completely dissociated[19]:

$$[R{-}CO]^{\oplus} = R^{\oplus} + CO$$

(1.419 Å)[58]. It can be concluded from these results as a whole that the value of 1.385(16) Å given by *Boer*[51] for the acetylium ion is too small.

The oxocarbenium ions can be described by the following series of resonance structures, which are given here for the methyloxocarbenium ion:

$$\underset{(a)}{CH_3{-}C{\equiv}\overset{\oplus}{O}} \leftrightarrow \underset{(b)}{CH_3{-}\overset{\oplus}{C}{=}O} \leftrightarrow \underset{(c)}{\overset{\oplus}{H}CH_2{=}C{=}O}$$

If one considers the environment of the oxocarbenium ions, one finds that the shortest distances to the anions $[MX_{n+1}]^-$ always occur between the carbon atom C(1) of the carbonyl group and the halogen atoms of the adjacent anions. As an example, Figure 3 shows the environment of the ethyloxo-

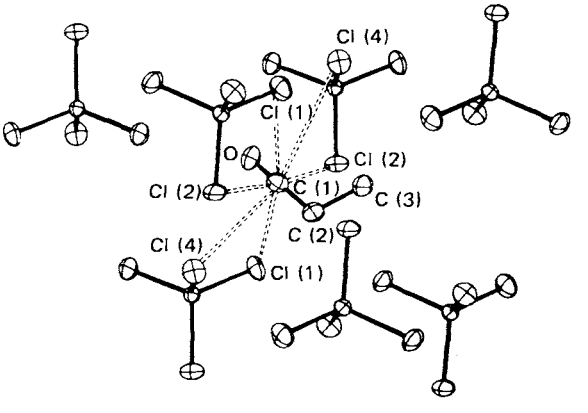


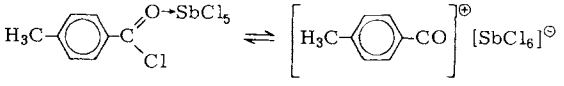
Fig. 3. Environment of the ethyloxocarbenium ion in the complex $[C_2H_5CO]^+[GaCl_4]^-$.

carbenium ion in the complex $[C_2H_5CO]^+[GaCl_4]^-$. The unusually short C(1)...Cl distances have been attributed to a decrease in the covalent radius of the C(1) atom as a result of its positive charge. Apart from this shorter distance, the arrangement of the ions in the lattice gives no evidence of any association of anions and oxocarbenium ions. Above all, the halogen atoms show no affinity for the oxygen atoms of the oxocarbenium ion, since the O...X distances in every case are greater than the sum of the van der Waals radii of these atoms. It therefore seems justifiable, in the description of the oxocarbenium ions, to place particular weight on the resonance structure *(b)* in which the positive charge is essentially localized on the carbon atom of the carbonyl group. It should be remembered in this connection that a positive partial charge was found on this carbon atom by NMR studies[19].

3.3. Coexistence of the Ionic and Molecular Forms

The vibrational spectra and the NMR spectra have shown that the two possible structures, *i.e.* the ionic and the molecular form, can exist together in solution for the same addition compound. Which of the two forms predominates depends on the solvent. A polar solvent with a high dielectric constant (ε) increases the concentration of the ionic form at the expense of the molecular form[15].

The influence of the solvent on the structure of the complex formed is particularly clear in the case of the addition compound of antimony pentachloride and *p*-toluoyl chloride. Thus *Chevrier, le Carpentier,* and *Weiss*[47] isolated two crystalline modifications. Rhombic crystals of the modification A were obtained from carbon tetrachloride, an apolar solvent ($\varepsilon = 2.2$), while the monoclinic modification B crystallizes from chloroform, a polar solvent ($\varepsilon = 5.05$). The crystal structures show conclusively that the modification A corresponds to the complex in its molecular form $4\text{-}CH_3—C_6H_4CClO \rightarrow SbCl_5$ and the modification B to the oxocarbenium salt $[4\text{-}CH_3—C_6H_4CO]^+[SbCl_6]^-$. Figure 4 shows the two structures in which this addition compound can exist in the solid state. It must be emphasized that the salt B can be obtained from a solution of the molecular form A in $CHCl_3$, and that conversely, the molecular form A can be isolated from a solution of the ionic form B in CCl_4. This result confirms that the two structures exist in equilibrium with each other in solution.



This equilibrium in solution must be expected for all addition compounds $MX_n \cdot R—COX$; the results of spectroscopic measurements cannot therefore be compared directly with the information obtained from X-ray diffraction, since the equilibrium may be displaced by recrystallization, with the result that the compound that is more stable in the solid state is isolated. It can often be seen even from the IR spectra of the solids that the ionic form and the molecular form are present together. This may be due to interactions between the complex and the support material, or the equilibrium may be displaced when part of the complex temporarily changes its state of aggregation. Thus according to their crystal structure, the adducts $AlCl_3 \cdot C_2H_5COCl$ and $AlCl_3 \cdot 2\text{-}CH_3—C_6H_4COCl$ are exclusively donor-acceptor complexes[42,44]; on the other hand, a predominantly ionic structure can be deduced from their IR spectra[15,42].

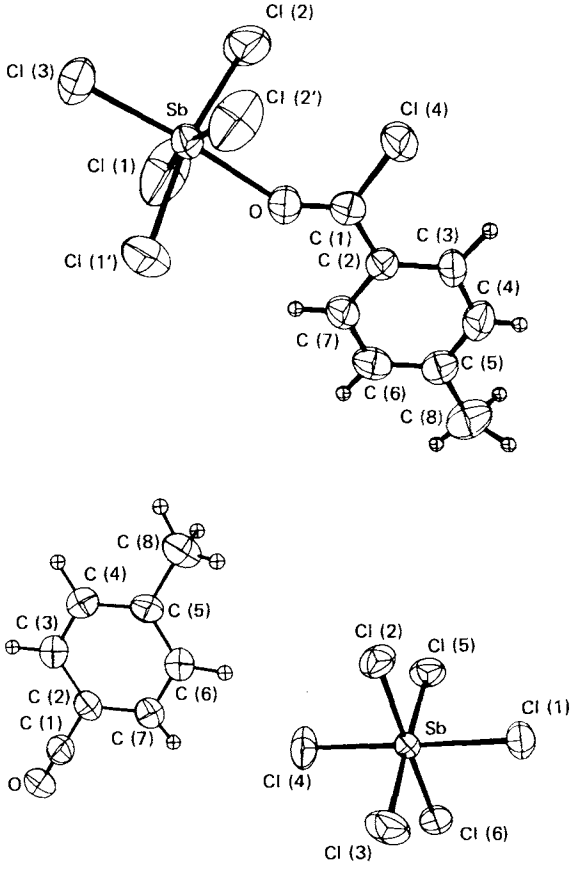


Fig. 4. The two isomeric structures of the complex $SbCl_5 \cdot 4\text{-}CH_3—C_6H_4COCl$: the molecular form (top) and the ionic form (bottom).

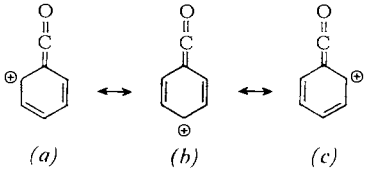
4. Electron Distribution in the Oxocarbenium Ions

Boer[51] has carried out an MO calculation of the electronic configuration of the $[CH_3CO]^+$ ion. He found a positive charge of +1.18e according to *Mulliken* for the carbon atom C(1) of the carbonyl group. The calculated charges for the other atoms are −0.35e for the oxygen atom, −0.11e for the carbon atom C(2) of the methyl group, and +0.07e for each of the hydrogen atoms. This last value in particular agrees well with that calculated for the hydrogen atoms in ethane, and leads to the assumption that the contribution of hyperconjugated forms in the methyloxocarbenium ion is probably negligible.

Rees, Veillard, and *Weiss*[59] recently compared the electron density distributions of the methyloxocarbenium ion $[CH_3CO]^+$ and of the isopropyloxocarbenium ion $[(CH_3)_2CHCO]^+$ with that of acetonitrile by a series of *ab-initio* calculations by the LCAO-MO-SCF method. Their results confirm that the positive charge in these oxocarbenium ions is essentially localized on the $p\pi$ orbitals of the carbon atom C(1) of the carbonyl group. Nevertheless, the total charge on the carbon C(1) (+0.60e) in the methyloxocarbenium ion is smaller than that calculated by *Boer* (+1.18e); however, it is offset in its immediate vicinity by a strong negative

charge of −0.58e on the carbon atom C(2). The ionic character of the bond C(1)—C(2) is even more pronounced in the isopropyloxocarbenium ion, in which the positive charge of the atom C(1) is higher (+0.73e); the charge on the atom C(2), on the other hand, is only slightly affected (−0.60e), though one would expect an inductive effect due to the methyl group. Optimization of the bond length C(1)—C(2) gave the value 1.45 Å, which is in excellent agreement with the value found experimentally for the ion $[CH_3CO]^+$ by *le Carpentier* and *Weiss*[52]. It should also be emphasized that the C(1)—C(2) bond in the methyloxocarbenium and isopropyloxocarbenium ions has no π-bond character, and that the optimization of the position of the hydrogen atoms in the $[CH_3CO]^+$ ion has led to the usual geometry of the methyl group. In other words, the contribution of the limiting resonance form *(c)* can be safely disregarded in the alkyloxocarbenium ions.

In aryloxocarbenium ions, on the contrary, the participation of resonance forms of this type is favored by the phenyl group, which allows much easier displacement of the positive charge than the methyl group.



(a) *(b)* *(c)*

Nucleophilic substituents in the *o* and *p* positions should help to stabilize this limiting form. This has in fact been observed for the 2-tolyloxocarbenium and 4-tolyloxocarbenium ions[47,54]. The C—C bonds lengths in these two ions, which are shown in Figure 5, support this assumption.

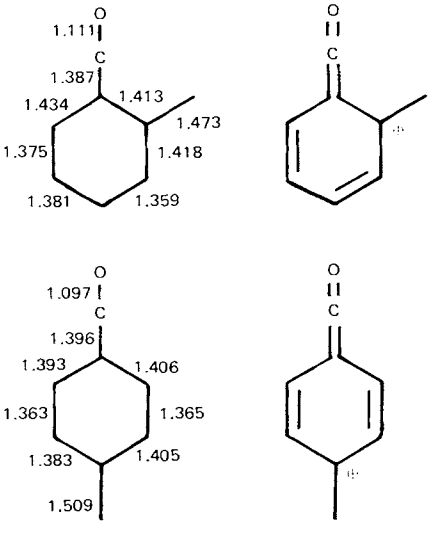


Fig. 5. Contribution of limiting resonance forms to the structure of aryloxocarbenium ions.

Recent investigations confirm the foregoing results. On the one hand the interpretation of the ^{13}C resonance in the phenyloxocarbenium ion and in some *o*-, *m*-, and *p*-substituted derivatives justifies the inclusion of the resonance structure *(c)*[41]. On the other hand, ESCA measurements have shown[60] that the difference between the energies of the 1s electrons of carbon atoms C(1) and C(2) is smaller in the aryloxocarbenium ions than in the alkyloxocarbenium ions. This can be attributed to the delocalization of the charge over the aromatic nucleus of the aryloxocarbenium ions.

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[1] *G. A. Olah:* Friedel-Crafts and Related Reactions. Interscience, New York 1963, Vol. 1, p. 91, 665.

[2] *C. A. Thomas, M. B. Moshier, H. E. Morris,* and *R. W. Moshier:* Anhydrous Aluminium Chloride in Organic Chemistry. Reinhold, New York 1941.

[3] *W. Hückel:* Theoretische Grundlagen der organischen Chemie. Akademie-Verlag, Leipzig 1956, 8. Edit., Vol. 1, p. 697.

[4] *P. Pfeiffer:* Organische Molekülverbindungen. Ferdinand Enke Verlag, Stuttgart 1927, 2. Edit.

[5] *H. Meerwein* and *H. Maier-Hüser*, J. Prakt. Chem. *134*, 51 (1932).

[6] *H. Kronberg*, J. Prakt. Chem. *61*, 494 (1900).

[7] *H. Meerwein*, Liebigs Ann. Chem. *455*, 227 (1927).

[8] *N. N. Lebedev*, J. Gen. Chem. USSR *21*, 1788 (1951).

[9] *W. Dilthey*, Ber. Deut. Chem. Ges. *71*, 1350 (1938).

[10] *G. Illari*, Gazz. Chim. Ital. *77*, 492 (1947).

[11] *B. P. Susz* and *J. J. Wuhrmann*, Helv. Chim. Acta *40*, 722 (1957).

[12] *G. A. Olah, S. J. Kuhn, W. S. Tolgyesi,* and *E. B. Baker*, J. Amer. Chem. Soc. *84*, 2733 (1962).

[13] *G. A. Olah*, Rev. Chim. Acad. Repub. Pop. Roum. *7*, 1139 (1962).

[14] *B. P. Susz* and *J. J. Wuhrmann*, Helv. Chim. Acta *40*, 971 (1957).

[15] *D. Cook*, Can. J. Chem. *37*, 48 (1959).

[16] *D. Cook*, Can. J. Chem. *40*, 480 (1962).

[17] *D. Cassimatis* and *B. P. Susz*, Helv. Chim. Acta *44*, 943 (1961).

[18] *D. Cassimatis* and *T. Theophanides*, Can. J. Spectr. *17*, 17 (1972).

[19] *G. A. Olah, W. S. Tolgyesi, S. J. Kuhn, M. E. Moffatt, I. J. Bastien,* and *E. B. Baker*, J. Amer. Chem. Soc. *85*, 1328 (1963).

[20] *B. P. Susz* and *D. Cassimatis*, Helv. Chim. Acta *44*, 395 (1961).

[21] *D. Cassimatis, P. Gagnaux,* and *B. P. Susz*, Helv. Chim. Acta *43*, 424 (1960).

[22] *J. C. Jaccard* and *B. P. Susz*, Helv. Chim. Acta *50*, 97 (1967).

[23] *G. A. Olah* and *M. B. Comisarow*, J. Amer. Chem. Soc. *89*, 2694 (1967).

[24] *G. A. Olah* and *M. B. Comisarow*, J. Amer. Chem. Soc. *88*, 3313 (1966).

[25] *G. A. Olah* and *M. B. Comisarow*, J. Amer. Chem. Soc. *88*, 4442 (1966).

[26] *B. P. Susz* and *I. Cooke*, Helv. Chim. Acta *37*, 1273 (1954).

[27] *B. P. Susz*, C. R. Acad. Sci. *248*, 2569 (1959).

[28] *I. Cooke, B. P. Susz,* and *C. Herschmann*, Helv. Chim. Acta *37*, 1280 (1954).

[29] *H. Hogeveen*, Rec. Trav. Chim. Pays-Bas *86*, 809 (1967).

[30] *G. A. Olah* and *A. M. White*, J. Amer. Chem. Soc. *89*, 3591 (1967).

[31] *G. A. Olah* and *A. M. White*, J. Amer. Chem. Soc. *89*, 4752 (1967).

[32] *G. A. Olah* and *A. M. White*, J. Amer. Chem. Soc. *89*, 7072 (1967).

[33] *A. Terenin, W. Filimonov,* and *D. Bystrov*, Z. Elektrochem. *62*, 180 (1958).

[34] *H. J. Coerver* and *C. Curran*, J. Amer. Chem. Soc. *80*, 3522 (1958).

[35] *G. C. Turrel* and *J. E. Gordon*, J. Chem. Phys. *30*, 895 (1958).

[36] *P. N. Gates* and *D. Steele*, J. Mol. Struct. *1*, 349 (1968).

[37] *D. Cassimatis, J. P. Bonnin,* and *T. Theophanides*, Can. J. Chem. *48*, 3860 (1970).

[38] *A. Germain, A. Commeyras,* and *A. Casadevall*, Bull. Soc. Chim. Fr. *8*, 3177 (1972).

[39] *H. Ulich, E. Hertel,* and *W. Nespital*, Z. Phys. Chem. (B) *17*, 21 (1932).

[40] *G. A. Olah, S. J. Kuhn, S. H. Flood,* and *B. A. Hardie*, J. Amer. Chem. Soc. *86*, 2203 (1964).

[41] *G. A. Olah* and *P. W. Westerman*, private communication.

[42] *J. M. le Carpentier* and *R. Weiss*, Acta Cryst. *B 28*, 1437 (1972).

[43] *S. E. Rasmussen* and *N. C. Broch*, Acta Chem. Scand. *20*, 1351 (1966).

[44] *B. Chevrier, J. M. le Carpentier,* and *R. Weiss*, Acta Cryst. *B 28*, 2659 (1972).

[45] *J. M. le Carpentier* and *R. Weiss*, Acta Cryst. *B 28*, 1442 (1972).

[46] *B. Chevrier, J. M. le Carpentier,* and *R. Weiss*, Acta Cryst. *B 28*, 2667 (1972).

[47] *B. Chevrier, J. M. le Carpentier,* and *R. Weiss*, J. Amer. Chem. Soc. *94*, 5718 (1972).

[48] *L. Brun* and *C. I. Bränden*, Acta Cryst. *20*, 749 (1966).

[49] *C. I. Bränden* and *I. Lindqvist*, Acta Chem. Scand. *17*, 353 (1963).

[50] *M. Bonamico, G. Dessy*, and *C. Ercolani*, Chem. Commun. *1966*, 24.
[50a] Cf. *G. A. Olah*, Angew. Chem. *85*, 183 (1973); Angew. Chem. internat. Edit. *12*, 173 (1973).
[51] *F. P. Boer*, J. Amer. Chem. Soc. *90*, 6706 (1968).
[52] *J. M. le Carpentier* and *R. Weiss*, Acta Cryst. *B 28*, 1421 (1972).
[53] *J. M. le Carpentier* and *R. Weiss*, Acta Cryst. *B 28*, 1430 (1972).
[54] *B. Chevrier, J. M. le Carpentier*, and *R. Weiss*, Acta Cryst. *B 28*, 2673 (1972).
[55] *B. Chevrier* and *R. Weiss*, unpublished results.
[56] *G. Herzberg:* Spectra of Diatomic Molecules. Van Nostrand, Princeton 1959, 2. Edit., p. 522.
[57] *C. C. Costain*, J. Chem. Phys. *29*, 864 (1958).
[58] *D. R. Lide*, J. Chem. Phys. *22*, 1577 (1954).
[59] *B. Rees, A. Veillard*, and *R. Weiss*, Theor. Chim. Acta *23*, 266 (1971).
[60] *G. D. Mateescu, J. L. Riemenschneider, J. J. Svoboda*, and *G. A. Olah*, J. Amer. Chem. Soc. *94*, 7191 (1972).

Biochemistry of Natural Proteinase Inhibitors

By Harald Tschesche[*]

The natural inhibitors of proteolytic enzymes are proteins. These inhibitors associate reversibly with the enzymes to form stoichiometric protein-protein complexes, in which substrate-analogous association at the active center of the enzyme results in competitive inhibition of all catalytic functions. The very widespread occurrence of inhibitors in the animal and plant kingdoms underlines their biological importance in the intermediate metabolism, which can be understood as an extension of the possibilities for temporary and local limitations of enzyme activities. Existing knowledge includes a series of covalent structures, detailed kinetic data on the reversible protein-protein interaction, the processes involved in inactivation, and chemical methods for the modification of these proteins. Early X-ray structural data for an inhibitor and its enzyme complex provide an insight into the molecular structure of the latter and the interactions involved in the association to form the complex.

1. Introduction

As early as the turn of the century, the occurrence of "antienzymes" was held responsible for the anti-trypsin activity of serum[1, 2] and for the resistance of nematodes to the digestive enzymes of their host organisms[3]. During the 1930's and 1940's *Kunitz* pioneered the isolation of the natural tissue trypsin inhibitor from bovine pancreas[4] and the inhibitor from soybeans[5, 6]. He demonstrated their protein nature, crystallized the proteins and their trypsin complexes[4], and started investigations on the stoichiometry of the enzyme-inhibitor association[4, 7]. Since then, with the aid of modern ion-exchange methods and affinity chromatography, many proteinase inhibitors have been concentrated and/or isolated from a variety of animal and plant tissues and characterized.

General interest in this field was stimulated less by the improved methods of protein chemistry than by the increased knowledge of the physiological, pharmacological, and food-technological significance of proteinases and their functions in normal and pathological processes in human and animal organisms. The function of proteolytic enzymes is by no means confined to the utilization of food protein, but plays a decisive part in the mobilization of tissue proteins, the activation of proenzymes, and the liberation of pharmacologically very active polypeptides such as the kinins (bradykinin, angiotensin, *etc.*) and peptide hormones (insulin *etc.*). Proteolytic enzymes also play a part in the control of blood coagulation and fibrinolysis and in inflammatory processes, immunobiological processes, and the fertilization process.

The naturally occurring inhibitors (*i.e.* inhibitors having a protein nature as opposed to low molecular weight, synthetic inactivators), as natural antagonists of proteinases, can intervene selectively in the multifarious occurrences of specific proteolytic processes in the organism.

The recognized molecular and biological principles for natural inhibitors of the endopeptide serine proteases, *i.e.* peptidyl peptide hydrolases, will be discussed in the present article. For many details, the reader is referred to the literature (on pharmacological[8, 9], food-physiological[10–12], molecular[13–24], and kinetic aspects[18–24]).

The discussion will not include inhibitors formed by immunobiological reactions and based on antigen-antibody interactions; bacterial peptide inhibitors from Penicillium[25] and Streptomyces species[26], the inactivating pepsinogen fragment[27], and inhibitors that are not proteins, such as the acidic polysaccharide heparin[28] and amino acid polycondensates[29], will also be excluded.

2. Occurrence

Proteinase inhibitors are of widespread occurrence in the animal and plant kingdoms. They have been isolated from seeds of Leguminosae (soybeans[5, 6], lima beans[8, 30], and other

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beans[8,12]) and grains (wheat[8,12,31] and rye[31]), as well as *e.g.* from potatoes[8,12,32], beets[8], nuts[8,12,33,74], corn[8,12,33], and peas[208]. However, their occurrence is not confined to the seeds[12,34]. They have recently also been isolated from bacteria (*Streptomyces albogriseolus*[224] and *Neurospora crassa*[225]).

A striking analogy with the plant seeds is the occurrence of proteinase inhibitors in the food protein (albumen) of many eggs in the animal kingdom. Thus proteinase inhibitors have been found as ovoinhibitors (with approx. 10% of carbohydrates) or as ovomucoids (with approx. 25% of carbohydrates) in the whites of the eggs of hens[8,17] and other birds[17,35] and in the secretion of the albumin glands of snails[36,37] and other molluscs[38].

The animal inhibitors, whose natural occurrence has been investigated in much greater detail, are found both in tissue and in secretions of organs. Thus the trypsin-kallikrein®[*] inhibitor from bovine organs (Kunitz inhibitor or kallikrein inactivator[39]) has been found exclusively as an intracellular component in the parotid gland, liver, lung[8,39], and pancreas[4]. The secretory trypsin inhibitor (Kazal inhibitor[40]), which, unlike the trypsin-kallikrein inhibitor, probably occurs in all mammals[8,41], is also formed in the pancreas, but is extruded with the proenzymes in the juice of the gland[41,42]. Many of the animal inhibitors are secretory proteins, such as the trypsin inhibitor of mammalian pancreas[41-45], of blood plasma[8,46] and seminal plasma[8,47,48,187], of milk and colostrum[13,15,16,50,77,179], of the submandibular glands[8,202], and of snails' slime[49].

Despite their different physiological functions, it is quite possible for tissue inhibitors and secretory inhibitors to be genetically related, as has been found for the trypsin-kallikrein inhibitor (Kunitz inhibitor) from bovine organs (58 amino acids, carbohydrate-free; cf. Figs. 5a, 6a, 11), the bovine colostrum inhibitor (67 amino acids with carbohydrate present; Fig. 5b)[50], and isoinhibitor K from snails (*Helix pomatia*, 58 amino acids, carbohydrate-free; Fig. 5c)[214,215], all of which have homologous structures.

The molecular weights of plant and animal inhibitors are mainly in the range from 5000 to 25000, but, as in the case of the inhibitors of human blood plasma, which belong to the group of α-globulins, they may also be of the order of 54000 (α_1-antitrypsin), 69000 (α_1-antichymotrypsin), and up to 160000 (inter-α-trypsin inhibitor), and in exceptional cases considerably higher (725000 for α_2-macroglobulin)[46,226].

3. General Properties

3.1. Assay of Inhibitors

Activities and concentrations of proteinase inhibitors are nowadays determined mainly by means of their complex formation with the enzymes, the decrease in the hydrolysis of natural or synthetic substrates being measured by enzyme-kinetic methods[51]. The methods are extremely sensitive, and allow the fast determination of microgram quantities of inhibitors. Sufficient preincubation of the enzyme and the inhibitor to enable the inhibition equilibrium to be reached is necessary for accurate determinations. When specific enzyme substrates are used, inhibitor concentrations can be determined even in crude tissue extracts, provided that the association constant of the enzyme and the inhibitor is high ($K_{ass} \approx 10^6$—10^7 l/mol) or the exact enzyme concentration is known. The difficulty that very pure enzymes are necessary for accurate determinations by kinetic methods can be overcome by the use of the "active site" titration reagents of *Chase* and *Shaw*[53] and *Kezdy* and *Kaiser*[52], since only active enzyme molecules are then determined. For reliable values of the specific inhibition activity, the measurements should be carried out at about 50% inhibition of the enzyme, provided that the inhibition proceeds stoichiometrically at least up to this range.

In addition to the enzymatic methods, methods based on the changes in physico-chemical parameters on complex formation have also been developed (for a survey see Ref.[19]).

3.2. Special Isolation Methods

Proteinase inhibitors, particularly the many low molecular weight proteins, are mostly extremely resistant to denaturation by acids and by heat. These remarkable properties were utilized by *Kunitz*[4] for the precipitation and separation of accompanying proteins during purification. In particular, they allow the dissociation of enzyme-inhibitor complexes with irreversible inactivation and precipitation of the proteinase. This also offers the possibility of separating inhibitors *via* their enzyme-inhibitor complexes, which are then decomposed. Both the free inhibitors and their complexes can be purified by molecular sieve filtration on gels, since the association constants are generally so high that the complexes migrate undissociated in neutral solution under the conditions of a gel exclusion chromatography, whereas at low pH values or in urea solutions they can be separated from the enzymes on the column.

The stability of the complex of the enzyme and the inhibitor makes affinity chromatography using resin-bound enzymes[54-59] an almost ideal purification method in the isolation of inhibitors[55]. With tissue and plant extracts that had undergone little preliminary purification, and even with organ fluids themselves as starting materials, *Fritz*, *Hochstrasser*, and *Werle* for the first time isolated a series of proteinase inhibitors from pancreas[43,55], corn and rye[56,60], seminal vesicles[55,57], and human sperm plasma[61]. Several inhibitors with different specificities can also be separated on suitable enzyme resin columns[57]. There is nothing to prevent the repeated use of the enzyme resins; in our laboratory, trypsin resins have been repeatedly used for isolation purposes over a period of a year. Subsequent purification of the preparations by ion-exchange chromatography is essential in most cases, since many extracts, particularly from plant materials, contain several inhibitors[8] or isoinhibitors[38,62,63]. Moreover, partial proteolysis of the "reactive site"[64] and (as in the case of the temporary inhibitors of the mammalian pancreas) modification by proteolytic cleavage of further peptide linkages[65,66] may be brought about by the active enzyme during the isolation process. The isolation of inhibitors by "classical" methods of protein chemistry in the presence of chemical enzyme inactivators such as diisopropyl fluorophosphate (DFP), benzamidine, or sulfonyl fluoride avoids these dangers and has been successfully used in particular in the isolation of pancreatic inhibitors directly from the pancreatic secretion by *Greene et al.*[42,44,45].

[*] Kallikrein is a registered trade mark of Bayer AG, Leverkusen. The name approved by the enzyme commission is kininogen (EC 3.4.21.8).

4. Inhibitory Behavior

4.1. Nature of the Inhibition

The inhibition of the esterolytic and proteolytic activities of the endopeptidases results from substrate-analogous attachment of the inhibitors to the active center of the enzyme. The competitive (or pseudocompetitive) character of the inhibition of enzymes by protein inhibitors, synthetic inhibitors, and specific substrates has been satisfactorily demonstrated[60-70].

Non-competitive inhibition has occasionally been deduced from Lineweaver-Burk diagrams. This type of inhibition occurs if $1/K_m$ for the substrate is very much smaller than K_{ass}[71] or if the dissociation of the enzyme-inhibitor complex (after the usual preincubation) is so slow that equilibrium is not reached within the period of the measurements[19].

4.2. Course of the Inhibition with Time

Whereas the majority of low molecular weight inhibitors, such as those from Ascaris[20, 21, 72], bovine organs[8, 13-21, 24], sea anemones[62], snails[63], leeches[73] or cuttle-fish or from plants such as soybeans[5, 6, 18-21] and lima beans[8, 30], nuts[33, 74], corn[33], potatoes[8, 12, 32] *etc.* cause permanent inhibition (Fig. 1a) of the proteolytic activity, the inhibition due to some inhibitors is effective only for a limited time. This phenomenon, which was first observed by *Gorini* and *Audrain*[75] for ovomucoid from hens' egg-white, was also found by *Laskowski Sr.* and *Wu*[76] for the secretory bovine inhibitor (Kazal inhibitor) and referred to as "temporary inhibition" (Fig. 1b). The reasons for this difference in behavior lie in the difference in the stabilities of the inhibitors (which are themselves proteins) toward proteolytic degradation by the proteinases initially inhibited by them[64, 65, 75-78]. In the case of the temporarily acting secretory pancreatic inhibitors of mammals, this special property could be of physiological significance (see Section 11).

In addition to permanent and temporary inhibition, a "progressive inhibition" has also been observed[46], particularly for the inhibitors of (human) blood plasma. Slow-acting and immediate-acting "antiplasmins" and "antithrombins" are found among the high molecular weight proteinase inhibitors of the α_1- and α_2-globulin fractions. Whereas the $C\bar{1}$ inactivator (MW 104000) and α_2-macroglobulin (MW 725000) inhibit plasmin immediately, the inactivation by α_1-antitrypsin is a slow, time-dependent reaction (Fig. 1c)[46]. However, α_1-antitrypsin and $C\bar{1}$ inactivator (and α_2-macroglobulin) also act as progressive inhibitors toward kallikrein[79, 80]. The inactivation rate increases with rising temperature, suggesting that this behavior could be due to a conformational change of the inhibitor molecule. Similar observations have been made for the inhibition of thrombin by α_2-macroglobulin and antithrombin III[46].

4.3. Association Constants K_{ass}

The constants for the association of the enzyme (E) and the inhibitor (I) to form the complex (C) in accordance with the simplified equation (see Section 6.1) $E + I \rightleftarrows C$ are relatively

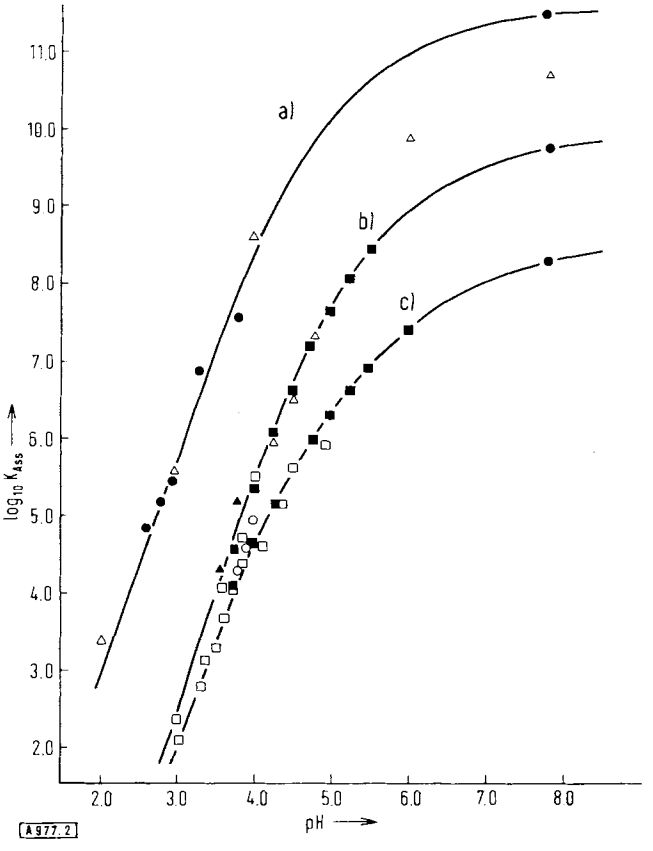


Fig. 2. pH dependence of the association constants K_{ass} for the association of bovine trypsin with a) the trypsin-kallikrein inhibitor (Kunitz inhibitor), b) the soybean inhibitor (Kunitz), c) hen ovomucoid, as found by the following measurement methods: ■ potentiometric, □ light scattering, △ gel chromatography, ▲ sedimentation, ● enzymatic residual activity, ○ fluorescence [19].

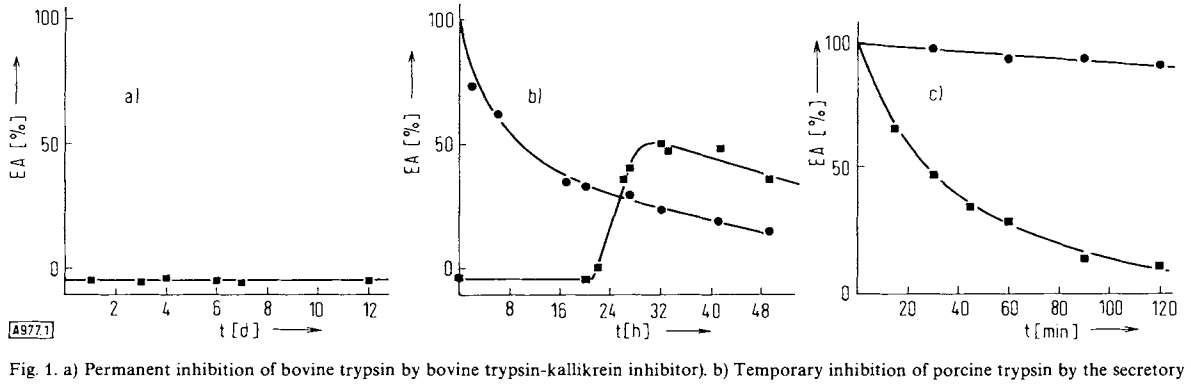


Fig. 1. a) Permanent inhibition of bovine trypsin by bovine trypsin-kallikrein inhibitor). b) Temporary inhibition of porcine trypsin by the secretory trypsin inhibitor I (Kazal type) from pig pancreas with an initial excess of inhibitor. c) Progressive inhibition of human plasmin by human α_1-antitrypsin [46]. (■ · · ■): enzyme activity of the enzyme-inhibitor solution, (● — ●): enzyme activity of the enzyme solution in the course of the autolysis. EA = enzyme activity, t = incubation time.

difficult to measure; they are much greater than those of the best substrates, and generally around 10^7 to 10^{14} l/mol, which corresponds to a free energy of association of 10 to 15 kcal/mol[67, 71]. For reliable values, the thermodynamic equilibrium of the complex formation must be reached[71], and the association constant must be greater than 10^8 l/mol, as is generally the case (for other methods for the determination of the association constants see Refs. [19, 81—85]).

The pH dependence of the association constants can be determined by the same methods. The association constant is found to change by 7 orders of magnitude (!) in the pH range from 2—6, whereas it only changes by a factor of 10 from pH 6 to pH 8 (Fig. 2). The enormously increased dissociation of the complexes at low pH values thus offers ideal conditions for the use of affinity chromatography in isolation processes.

5. Reactive Site

5.1. Reactive Site—Definition

The reactive site of the inhibitors is defined as the part of the molecule that enters into direct molecular contact with the active center of the enzyme on formation of the enzyme-inhibitor complex. The amino acid side chain responsible for the substrate-analogous accommodation in the specificity pocket of the enzyme is that of the "reactive amino acid residue" P_1; if the notation of *Schechter* and *Berger* is used here for the reactive site of proteinase inhibitors[86, 87].

$H_2N\text{-}P_x\text{----}P_4\text{-}P_3\text{-}P_2\text{-}P_1\text{-}P'_1\text{-}P'_2\text{-}P'_3\text{-}P'_4\text{----}P'_x\text{-}COOH$

The inhibitors of the enzyme trypsin and of the enzymes plasmin, kallikrein, acrosin, and silkworm cocoonase, which are similar to trypsin in their cleavage specificity, have arginine[17–19, 48, 62, 63, 89, 90] or lysine[17–19, 64, 88–90] as the "reactive amino acid residue" P_1, whereas alanine, leucine, isoleucine, and serine have been found as the amino acid residue P'_1. The activity and specificity of the inhibitors is retained on replacement of arginine by lysine (or *vice versa*), as is shown by the homology of the sequences in the reactive sites of the secretory pancreatic inhibitors of cattle[91], sheep[33, 92] (arginine inhibitors) and pigs[92] (lysine inhibitors) and by the results of the "enzymatic replacement reaction" on the soybean inhibitor[93] (see Section 6.3) and the occurrence both of arginine and of lysine in the isoinhibitors of snails[94], cuttlefish[38], and garden beans[210]. In all the trypsin inhibitors whose covalent structures have been established (see Section 8.2), the reactive site $P_1\text{-}P'_1$ is situated in a loop closed by a disulfide bridge, as had been postulated by *Ozawa* and *Laskowski, Jr.*[88]. The inhibitors thus become "cyclic substrates".

By analogy with the trypsin inhibitors, the amino acids tryptophan, tyrosine, phenylalanine, and leucine were to be expected as the residue P_1 in chymotrypsin inhibitors, according to the specificity of this enzyme. Leucine was found in the reactive sites of the chymotrypsin inhibitors from soybeans (*Bowman-Birk*)[74, 128, 228–230] and from lima beans[30]. A corresponding change in specificity as a result of a Lys↔Leu exchange was shown to be probable for both inhibitors, since corresponding homologous sequence regions have been found (see Section 8.1). This mutation appears to be a sufficient but by no means always necessary condition for the change in specificity, since association and inhibition of chymotrypsin has also been observed for "reactive sites" of the trypsin type[95, 96, 213].

In an enzymatic replacement reaction (see Section 6.3), *Leary* and *Laskowski, Jr.*[211, 212] replaced Arg^{63} by Trp^{63} in the reactive site of the soybean inhibitor (Kunitz) and hence brought about the conversion from trypsin to chymotrypsin specificity.

5.2. Partial Proteolysis

In a series of elegant experiments on the soybean inhibitor (Kunitz) *Laskowski, Jr. et al.*[18, 19] demonstrated that the peptide linkage $\text{-}P_1\text{-}P'_1\text{-}$ in the reactive site can be partially hydrolyzed in the course of the inhibition in the same way as hydrolysis takes place in a substrate. "Partial" means here that only some of the $\text{-}P_1\text{-}P'_1\text{-}$ linkages are hydrolyzed. Proteolysis at the reactive site of the native inhibitor with a single-stranded polypeptide chain ($I\text{-}P_1\text{-}P'_1$-intact) converts the protein into a modified inhibitor (I*, $\text{-P-COO}^{\ominus}$ $H_3\overset{\oplus}{N}\text{-P'}$-hydrolyzed). The native and the modified inhibitor have similar activities and specificities as inhibitors, and similar association constants[97]. The modifying partial proteolysis is based on the establishment of a stationary thermodynamic equilibrium, which can be brought about by catalytic quantities of enzyme (trypsin[97] or chymotrypsin[96]). The native inhibitor and the modified inhibitor react with the enzyme to form the same stable enzyme-inhibitor complex C[98, 99], which can dissociate again to give either the free enzyme and the native inhibitor or the free enzyme and the modified inhibitor. The reversibility of the equilibrium, *i.e.* the resynthesis of the peptide linkage $\text{-}P_1\text{-}P'_1\text{-}$ in the active site of the modified soybean inhibitor with formation of native inhibitor by catalytic quantities of enzyme (2 mole %), has been demonstrated by *Niekamp, Hixson, Jr.*, and *Laskowski, Jr.*[99] (see Section 6.3).

The equilibrium constant $K_{hyd}=[I^*]/[I]$ for the stationary equilibrium between the native and the modified inhibitor is strongly dependent on the pH (Fig. 3), with a minimum at pH = 6—7 and high values for the cleavage of the peptide

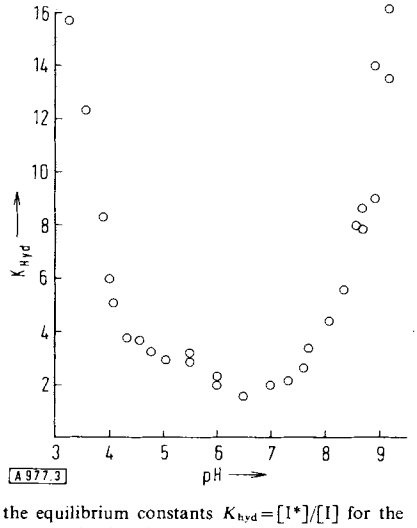


Fig. 3. pH dependence of the equilibrium constants $K_{hyd}=[I^*]/[I]$ for the equilibrium of the partial proteolysis of native (I) to modified (I*) soybean inhibitor (Kunitz) [19]. Somewhat improved data have recently been published from the same laboratory [227].

linkage -P_1-P'_1- in acidic solutions at pH = 3—4[118]. It thus proceeds as a special "substrate" hydrolysis at a very unphysiological pH value at which normal proteins are not hydrolyzed. The partial proteolysis has been demonstrated for a series of proteinase inhibitors[18,19,33,48,64,74,96,98,100,101,232–234] and used identification of the reactive sites. The degree of hydrolysis was estimated by analytical polyacrylamide gel electrophoresis[99] or by removal of the new C-terminal basic residue P_1 with carboxypeptidase B[88,100] or by Edman degradation and quantitative mass-spectral determination of the new N-terminal residue P'_1[101], though the reversibility of the proteolysis has been demonstrated in very few cases. The thermodynamic equilibrium may lie far over on the side of the broken peptide linkage as in the case of the soybean inhibitor (Kunitz), with 86% of modified inhibitor, or it may lie predominantly on the side of the native inhibitor, as in the case of the secretory pancreatic inhibitors, with approximately 25% modification.

The trypsin-kallikrein inhibitor (Kunitz) from bovine organs, in which no direct modification by trypsin has so far been observed, may be regarded as an extreme case. According to *Kress*, *Wilson*, and *Laskowski*, *Sr.*[102], however, this inhibitor is also hydrolyzed at the reactive site and at other peptide linkages after selective reduction of the disulfide bridge Cys^{14}-Cys^{38} (see Section 10). A trypsin-kallikrein inhibitor (Kunitz) modified only at the reactive site, which cannot be obtained directly by partial proteolysis with trypsin, has been synthesized indirectly *via* a series of chemical and enzymatic reactions by *Jering* and *Tschesche*[213]. This synthetic modified inhibitor is active toward trypsin, and is completely converted back into the native ("virgin") inhibitor by catalytic quantities of trypsin[213] and of chymotrypsin[231].

6. Mechanisms

6.1. Mechanism of Association

As a result of the partial proteolysis, a modified protein (I*) still possessing the full biological activity is formed from the native inhibitor (I). In the case of the system β-trypsin/soybean inhibitor (Kunitz), which has been studied in detail by *Luthy*, *Praissmen*, *Finkenstadt*, and *Laskowski*, *Jr.*[97], a very different reaction rate constant for the complex formation (L*→C) is found for the modified inhibitor (I*). The complex formation of I* must therefore also be taken into account for the thermodynamic equilibrium of the association of trypsin (T) and the inhibitor (I or I*) in the steady state. The complete system is therefore represented by eq. (1)[97]:

$$T + I \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} L \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} C \overset{k_3}{\underset{k_{-3}}{\rightleftharpoons}} L^* \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} T + I^* \qquad (1)$$

Eq. (1) represents the formal minimal mechanism, in which L and L* are loosely associated, non-"covalent" enzyme-inhibitor complexes (see Section 8.4). The existence of other intermediates is conceivable. The intermediates L and L* have been detected; it has been shown[97] that the equilibrium constants $K_L = k_{-1}/k_1$ and $K_{L^*} = k_4/k_{-4}$ are probably equal, whereas very different values with very similar pH dependence were found for the analogous rate constants k_2 and k_{-3}. Rapid establishment of the preliminary equilibrium with formation of the intermediate L was found, with $k_{-1} \gg k_2$[97]. Eq. (1) corresponds to the usual mechanism for the reversible substrate hydrolysis by serine hydrolases, the only formal difference being that no dissociation of the acylenzyme complex with liberation of the enzyme nucleophile occurs, since the inhibitors form only one reaction product, *i.e.* the complex C.

This two-step process for the complex formation is supported by the concentration-dependent transition from a second order to a first order reaction[97]. The initial loose association $T + I \xrightarrow{k_1} L$, which is probably a diffusion-controlled second order reaction, is followed by the non-diffusion-controlled complex formation $L \xrightarrow{k_2} C$ in a first order reaction. The fact that the second order rate constants for the association of trypsin and soybean inhibitor (Kunitz) are independent of the viscosity of the solvent had already led *Haynes* and *Feeney*[89] to the conclusion that the complex formation is not based on a diffusion-controlled process.

A series of findings indicate that the formal mechanism proposed for the β-trypsin/soybean inhibitor (Kunitz) system is generally valid. A comparative study with α-trypsin[97] gave the same first order rate constant k_2 for the reaction L→C as for β-trypsin. The association constant of the loose Michaelis complex L between α-trypsin and native inhibitor I, however, is an order of magnitude smaller than that of β-trypsin; $K_{L\alpha} = 10 K_{L\beta}$. This result corresponds to the lower stability of the complexes of α-trypsin with soybean inhibitor (Kunitz)[103,104], trypsin-kallikrein inhibitor (Kunitz) from bovine organs[104], and hen ovomucoid[105]. More kinetic data concerning the association of enzyme and inhibitors are given in Refs. [150, 244—248].

6.2. Kinetically Controlled Dissociation

If eq. (1) is generally valid, the same product, *i.e.* the stable enzyme-inhibitor complex C, is obtained regardless of whether it is prepared from the native or the modified inhibitor and the enzyme. Under conditions such that a sudden dissociation of the complex is forced (kinetically controlled dissociation), such as rapid adjustment of the pH to 2[98] or introduction of the complex into 6 M guanidinium chloride[93] in neutral solution, the products will be determined only by the relative values of the dissociation rate constants k_{-2} and k_3, and not by the position of the thermodynamic equilibrium between the native and the modified inhibitor. Since the rate constants for the conversion of the modified inhibitor (I*) into the native inhibitor (I) are generally much higher than for the reverse reaction, the kinetically controlled dissociation of the complex leads one to expect predominantly native inhibitor. Corresponding results were obtained for the kinetically controlled dissociation of the trypsin complexes from native and modified soybean inhibitor (Kunitz) by *Finkenstadt* and *Laskowski*, *Jr.*[98] and *Sealock* and *Laskowski*, *Jr.*[93], as well as for the dissociation of the trypsin complex from trypsin-modified Bowman-Birk soybean inhibitor and for the dissociation of the chymotrypsin complex from chymotrypsin-modified Bowman-Birk soybean inhibitor by *Frattali* and *Steiner*[106]. Predominantly native inhibitor was found in every case, though the equilibrium in both cases lies mainly on the side of the modified inhibitor.

The resynthesis of the broken peptide linkage -P_1-P'_1- in the modified inhibitor by complex formation with subsequent

kinetically controlled complex dissociation shows that the relation $k_{-2} \gg k_3$ is valid for these systems. It further follows that the dissociation rate constants $K_D = k_{-2} + k_3 \approx k_{-2}$ must roughly correspond to the complex dissociation constants k_{-2}.

It is interesting to note that the kinetically controlled resynthesis of the broken peptide linkage -P_1-P'_1- in the modified inhibitor is the best evidence at present for the reactive site of the inhibitor.

6.3. Enzymatic Replacement Reaction

By skillful combination and using the relationships given by the thermodynamic and kinetic constants, *Sealock* and *Laskowski, Jr.*[93] managed to replace the reactive amino acid residue arginine-63 in the soybean inhibitor (Kunitz) by lysine in a series of enzymatic reactions, and were thus able to demonstrate the fundamental equivalence of arginine and lysine as amino acid residues P_1 in the reactive sites of trypsin inhibitors, which had already been shown to be probable for homologous inhibitors.

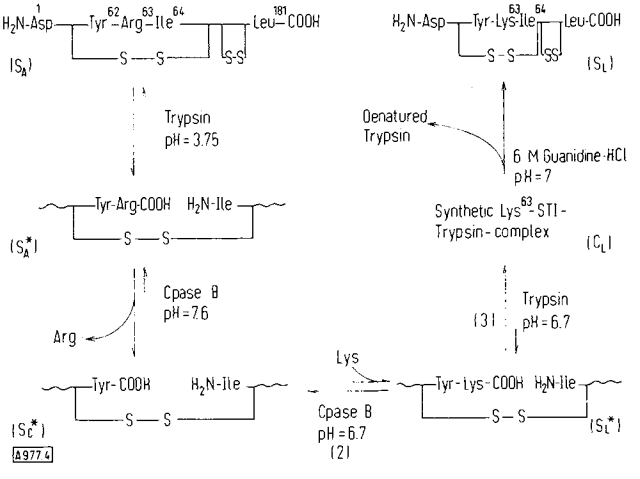


Fig. 4. Reaction steps in the course of the "enzymatic replacement reaction". The position of the equilibrium is qualitatively denoted by the relative size of the arrows [93]. Cpase = carboxypeptidase; STI = soybean trypsin inhibitor; S_A = native soybean inhibitor (Kunitz); S_A^* = modified inhibitor; S_C^* = de-Arg^{63} modified inhibitor; S_L^* = modified synthetic Lys^{63} inhibitor; C_L = trypsin complex with synthetic Lys^{63} inhibitor; S_L = intact synthetic Lys^{63} inhibitor.

Corresponding to the scheme in Figure 4, modified soybean inhibitor (peptide linkage Arg^{63}-Ile^{64} broken) (S_A^*) was converted into de-Arg^{63} modified inhibitor (S_C^*) with carboxypeptidase B, with loss of the inhibitory activity. On subsequent incubation with an excess of lysine and carboxypeptidase B [eq. (2)], the thermodynamically unfavorable enzymatic incorporation of lysine is coupled with the thermodynamically strongly favored complex formation of once again active Lys^{63} modified inhibitor (S_L^*) [eq. (3)]. Since the de-Arg^{63} modified inhibitor (S_C^*) does not form strong complexes with trypsin, the coupling of the two reactions and the displacement of the equilibrium can be forced [eq. (4)]. The synthetic Lys^{63} soybean inhibitor is isolated in the form of the trypsin complex (C_L) and subjected to kinetically controlled dissociation. "Native" Lys^{63} inhibitor (peptide linkage Lys^{63}-Ile^{64} intact) (S_L) is isolated as the reaction product[18,19,93].

Incubation of the synthetic Lys^{63} inhibitor with catalytic quantities of trypsin at pH = 3.75 led in a *slow* reaction to an

$$S_C^* + \text{Lys} \xrightleftharpoons{\text{Cpase B}} S^* \qquad K = 10^{-2}\ \text{l/mol} \qquad (2)$$

$$S^* + T \rightleftharpoons C_L \qquad K = 10^{9}\ \text{l/mol} \qquad (3)$$

$$S_C^* + \text{Lys} + T \rightleftharpoons C \qquad K = 10^{7}\ \text{l/mol} \qquad (4)$$

inhibitor that was electrophoretically indistinguishable from modified authentic Arg^{63} inhibitor[19]. The values of K_{hyd} for the hydrolysis of the peptide linkage -P_1-P'_1- in the reactive site of the Lys^{63} and Arg^{63} inhibitors thus appear to be equal; this demonstrates the thermodynamic equivalence of arginine and lysine. According to observations by *Sealock* and *Laskowski, Jr.*[19,93] on Arg^{63} and Lys^{63} soybean inhibitors and by *Tschesche* and *Obermeier*[101] on homologous lysine and arginine inhibitors of the pancreas (Kazal type), however, the rates of the reactions with trypsin are lower by a factor of about 10 for lysine inhibitors.

The enzymatic arginine↔lysine exchange leads to homologous proteins such as would correspond to the gene products after a mutation of the Arg^{63} DNA codon to the Lys^{63} DNA codon. The biological realization of such arginine↔lysine or lysine↔arginine mutations in reactive sites of the inhibitors has been found in the sequencing of the secretory pancreatic inhibitors (see Section 8.1), and also appears from initial observations to occur within the same species in the secretory isoinhibitors of snails[94] and of garden beans[210]. To emphasize this analogy between biological mutation and enzymatic replacement reactions, *Laskowski, Jr.* (with every reservation) coined the term "enzymatic mutation"[19].

The same reaction scheme was used by *Leary* and *Laskowski, Jr.*[211,212] for the enzymatic replacement of Arg^{63} with Trp^{63} by incubation of the de-Arg^{63} modified inhibitor (S_C^*) with excess tryptophan and carboxypeptidase A in the presence of chymotrypsin. After kinetically controlled dissociation of the chymotrypsin complex, native Trp^{63} soybean inhibitor, which strongly inhibits chymotrypsin (see Section 5.1), was isolated as well as de-Arg^{63} modified inhibitor.

7. Chemical Modification

Chemical modifications at the reactive side chains of bifunctional amino acids of inhibitors have been used in large numbers to study the association and to characterize the reactive sites. The possibilities offered by this method can be illustrated by a number of examples (see also Ref. [19]).

Contrary to previous observations[107], we have found that the removal of the positive charge from the side chain of the basic amino acid residue P_1 in the reactive site of lysine inhibitors by deamination does not inactivate the trypsin-kallikrein inhibitor from bovine organs[108]. Pure loss of the charge, with no additional steric effect, rules out the ionic interaction of the side chain with the negative charge of Asp^{189}[*] in the specificity pocket of trypsin[109]. Steric effects such as the lengthening of the side chain of the basic residue P_1 (by approx. 1.5 Å) appear to reduce the activity even when the positive charge is retained, as seems to be shown, according to *Haynes* and *Feeney*, by the reduced activity of a series of guanidinated lysine inhibitors[89]. However, this is contradicted by the observations of *Kassell* and *Chow*[110] on the guanidination (and amidination) of the trypsin-kallikrein inhibitor (Kunitz) from bovine organs.

Elimination of the charge on the side chain with a simultaneous increase in size is brought about in lysine inhibitors by acylat-

ing reagents such as maleic anhydride or citraconic anhydride and in arginine inhibitors by dicarbonyl reagents such as butanedione, cyclohexanedione, and phenylglyoxal, and leads to inactivation of the inhibitors[89, 111]. This method has been used by *Fritz et al.*[111] for the classification of a large number of inhibitors as lysine or arginine inhibitors, and has proved generally useful for rapid preliminary studies. *Kowalski* and *Laskowski, Jr.*[112] recently also used this method for the determination of the constants $K_{hyd}=[I^*]/[I]$ (see Section 5.2) for modified inhibitors, since the acylation of the newly formed α-amino group on the residue P'_1 generally inactivates the modified soybean inhibitor, and probably modified proteinase inhibitors in general. However, this method can be applied to lysine inhibitors only after their guanidination.

As was first shown by *Chauvet* and *Acher*[90] in the identification of the reactive site (Lys^{15}-Ala^{16}) of the trypsin-kallikrein inhibitor (Kunitz) by polyalanylation with the *N*-carboxy anhydride of DL-alanine, at lysine residues 26, 41, and 46 in the trypsin-inhibitor complex can react with acylating agents without forcing the complex to dissociate, without simultaneous partial or complete acylation of the lysine residue 15 (P_1), and/or without deactivation of the recovered substituted inhibitor. Making use of this high stability of the complex, *Fritz, Schult, Meister*, and *Werle*[113] and *Tschesche, Jering*, and *Schorp*[114] were able to prepare acylated active or reactivable derivatives of the trypsin-kallikrein inhibitor (Kunitz), which have the same biological activity and specificity but completely different physiological behavior in the circulation (kidney function *etc.*) and other physico-chemical constants (isoelectric point *etc.*).

By nitration of tyrosine residues in the immediate neighborhood of the reactive site -P_1-P'_1- in the free inhibitor and in the inhibitor fixed in the complex, it is possible to determine their steric accessibility and hence their possible masking. The size of the contact site can thus be estimated, particularly if these results are supplemented by spectrophotometric titrations and p*K* determinations on the corresponding *o*-nitrotyrosines for the free inhibitor and for the inhibitor bound in the complex[92, 103].

Since the contact area generally involves only a few amino acid residues of the reactive site, it is understandable that the biological activity is not affected by removal of some residues from the amino terminal end, provided that this does not lead to a change in the residual structure and that the reactive site is not directly degraded. According to *Kassell* and *Chow*[110], guanidinated trypsin-kallikrein inhibitor (Kunitz) is fully active after Edman degradation of the N-terminal tripeptide. The same is true of the secretory pancreatic inhibitor I of pigs, which does not lose its activity on removal of the N-terminal tetrapeptide[44, 45, 115] or pentapeptide[66].

8. Structure of the Proteinase Inhibitors

8.1. Amino Acid Sequences and Homologies

The primary structure of the therapeutically interesting trypsin-kallikrein inhibitor (Kunitz) from bovine organs (Fig. 5a) has been established by *Kassell* and *Laskowski, Sr.*[116]; the structure was confirmed by *Chauvet* and *Acher*[117], by *Dlouhá, Pospíšilová, Meloun, and Šorm*[118], and by *Anderer* and *Hörnle*[119] (kallikrein inactivator[39] from bovine lung with Asn^{50} instead of Asp^{50}).

An interesting feature is the homology of more than 40% with bovine colostrum inhibitor, whose sequence was established by *Čechová, Jonáková*, and *Šorm*[50] (Fig. 5b); it contains an additional nine amino acids and a glycoprotein fraction.

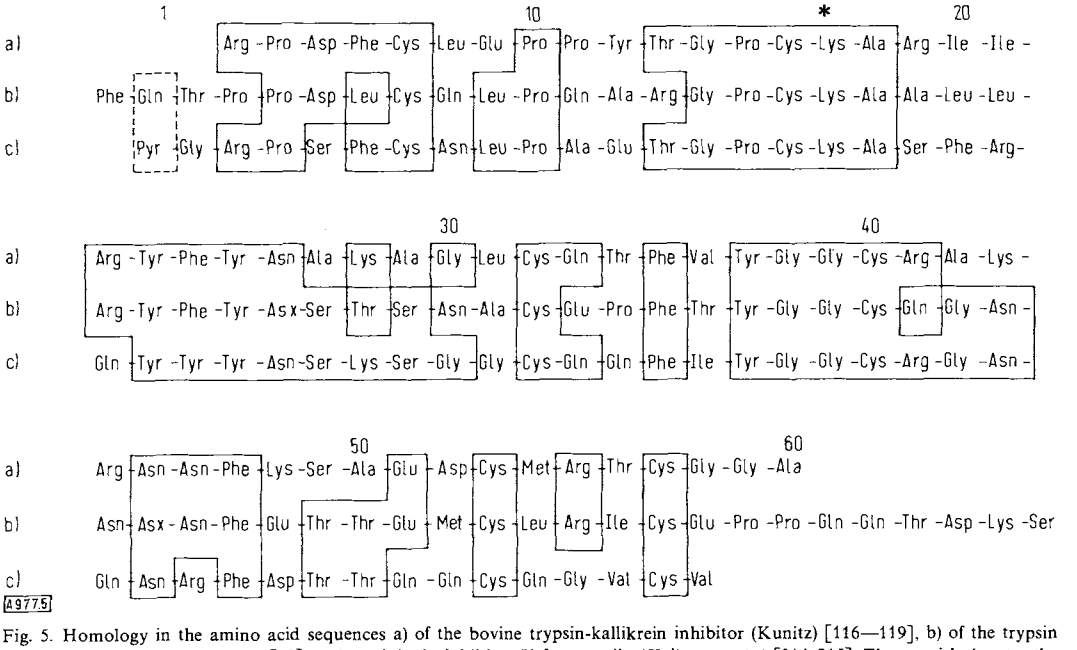


Fig. 5. Homology in the amino acid sequences a) of the bovine trypsin-kallikrein inhibitor (Kunitz) [116—119], b) of the trypsin inhibitor from bovine colostrum [50], and c) of the isoinhibitor K from snails *(Helix pomatia)* [214, 215]. The asterisk denotes the reactive site. Other proteins homologous to these inhibitors have recently been elucidated: d) Snake venom proteinase inhibitor II (from *Vipera russelli)* by *Takahashi, Iwanaga, Hokama, Suzuki*, and *Kitawaga* [236]. f) Proteinase inhibitor from turtle egg white by *Laskowski, Jr. et al.* [237] (partial sequence).

The genes of the two inhibitors evidently have a common phylogenetic origin, though the colostrum inhibitor must be regarded as a secretory protein, whereas the homologous trypsin-kallikrein inhibitor occurs only intracellularly in tissue

[*] The amino acids in trypsin were numbered as in chymotrypsinogen A; see *K. A. Walsh* and *H. Neurath*, Proc. Nat. Acad. Sci. USA *52*, 884 (1964); *O. Mikes, V. Tomašek, V. Holeysovsky*, and *F. Šorm*, Biochim. Biophys. Acta *117*, 281 (1966); *B. S. Hartley* and *D. M. Shotton* in *P. D. Boyer*: The Enzymes, Academic Press, New York 1971, vol. 3, 3rd ed., p. 323.

and has been found in many bovine organs. While colostrum inhibitors probably occur in many mammals and have so far been detected in cattle and pigs[77, 179], the trypsin-kallikrein inhibitor has been found only in a limited number of ruminants (cattle and sheep).

points to a common source gene for this inhibitor with a particularly broad specificity.

Another remarkable feature is that the bovine trypsin-kallikrein inhibitor (Fig. 6a) shows no homology with the secretory bovine pancreatic inhibitor (Kazal) (Fig. 6b), whose sequence

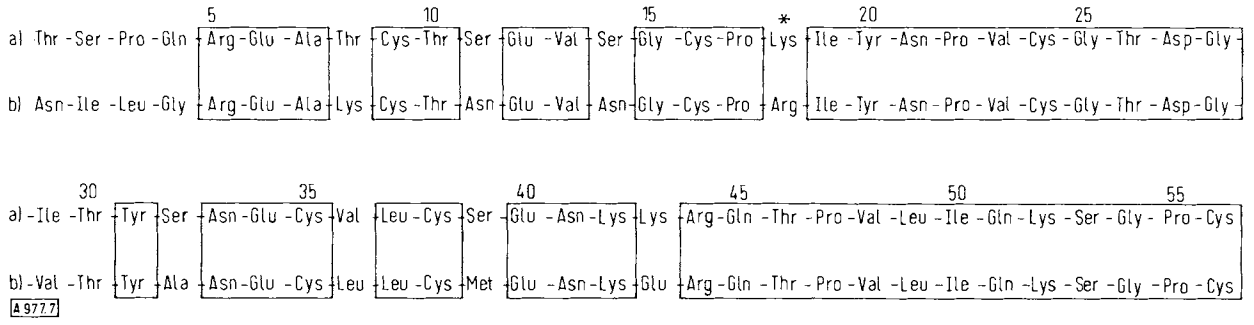


Fig. 7. Homology in the amino acid sequences of the secretory pancreatic inhibitors a) of pigs (inhibitor I) and b) of sheep [92]. The asterisk denotes the reactive site. The ovine inhibitor could be shown to be identical in amino acid sequence to the bovine inhibitor [91] (Fig. 6b) except for Ala^{32} which is Ser in the bovine species. Similar homologies have been found in the human inhibitor by *Greene* and *Bartelt* [238].

The amino acid sequence of the isoinhibitor K from the edible snail (*Helix pomatia*, Fig. 5c) was established by *Tschesche* and *Dietl*[214, 215]. This isoinhibitor surprisingly has the same degree of homology with the bovine trypsin-kallikrein inhibitor (Kunitz) as the bovine colostrum inhibitor. This agreement despite the great phylogenetic separation of cattle and snails

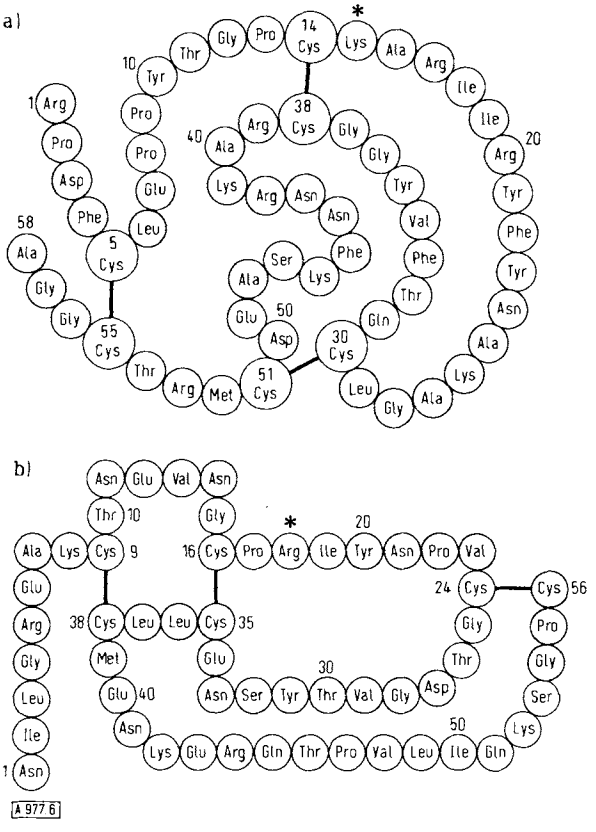


Fig. 6. Comparison of the complete covalent structures of a) the bovine trypsin-kallikrein inhibitor (Kunitz) [116—119] and b) the secretory trypsin inhibitor (Kazal) from bovine pancreas [91, 134, 135]. The asterisk denotes the reactive site. The disulfide bridges of the trypsin-kallikrein-inhibitor were determined by *Kassell* and *Laskowski, Sr.* [116] and confirmed by *Anderer* and *Hörnle* [119] on the inhibitor from bovine lung; those of the secretory trypsin inhibitor were determined by *Guy, Shapanaka*, and *Greene* [134, 135] and confirmed on the porcine inhibitor by *Tschesche* and *Schneider* [92, 136].

was established by *Greene, Giordano*, and *Bartelt*[91]. This is underlined by the general differences in the physiological functions of the two inhibitors, which are also reflected in different specificities, in the inhibitory behavior, and in the sites of their cellular biosynthesis.

The primary structures of the pig pancreatic inhibitors (I, Fig. 7a, and II) have been elucidated by *Tschesche* and *Wachter*[45, 115, 120] and confirmed by *Bartelt* and *Greene*[121]. *Hochstrasser* and *Werle et al.*[33, 122] and *Tschesche* and *Obermeier*[92] determined the sequence of the inhibitor from sheep (Fig. 7b). A comparison of all the structures that have been established so far provides a preliminary picture of the invariant sequences and of the sequences that can be varied by exchange of individual amino acids. The high variability at the amino end agrees with the unimportance of this part of the sequence to the biological activity[44, 45, 66, 92, 123] and to the correct folding and renaturing after reduction and reoxidation[125]. The remarkable $Arg^{18} \leftrightarrow Lys^{18}$ mutation for the residue P_1 at the reactive site has already been mentioned (see Section 5.1); apart from this, no amino acid exchange is observed in this region (residues 15—28) or in the C-terminal part (residues 44—56).

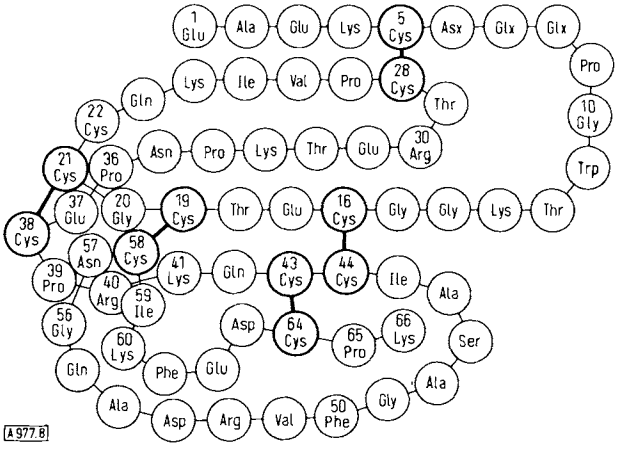


Fig. 8. Complete covalent structure of the inhibitor from *Ascaris lumbricoides* according to *Induni* [137].

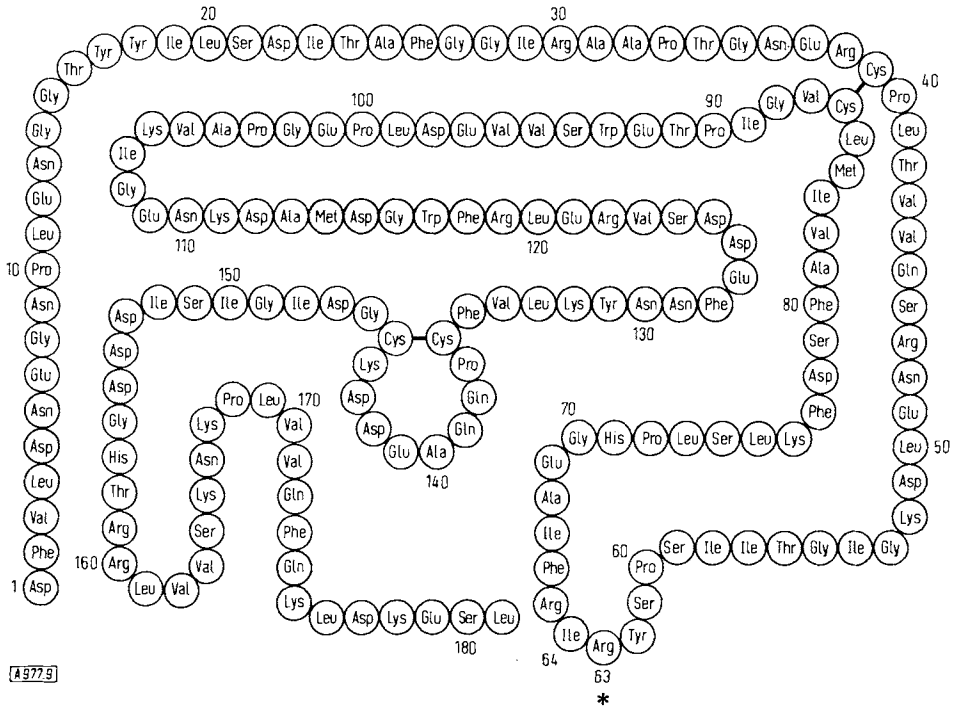


Fig. 9. Complete covalent structure of the trypsin chymotrypsin inhibitor from soybeans (Kunitz) according to *Koide, Tsunazawa*, and *Ihenaka* [126, 240, 241]. The asterisk denotes the reactive site.

The sequence of a trypsin-chymotrypsin inhibitor isolated by *Portmann* and *Fraefel*[124] (cf. [3]) from pig Ascarides has been elucidated by *Fraefel* and *Acher*[125] (Fig. 8). No pronounced homology with the animal inhibitors mentioned so far is found, except in the partial sequences Thr-Tyr-Gly-Gly-Cys-Glu (residues 37—42) in the bovine colostrum inhibitor and the similar sequence Thr-Lys-Gly-Gly-Cys-Glu (residues 12—17) in the Ascaris inhibitor.

A series of primary structures of plant inhibitors have recently also been determined. The complete sequence of the soybean inhibitor (Kunitz) (181 amino acids) was determined by *Koide, Tsunasawa*, and *Ikenaka*[126,240,241] (Fig. 9). It shows no homology with the second inhibitor from soybeans, *i.e.* the Bowman-Birk inhibitor[127] (71 amino acids), whose sequence was established by *Odani, Koide*, and *Ikenaka*[128] (Fig. 10a). On the other hand, extensive homology with this inhibitor

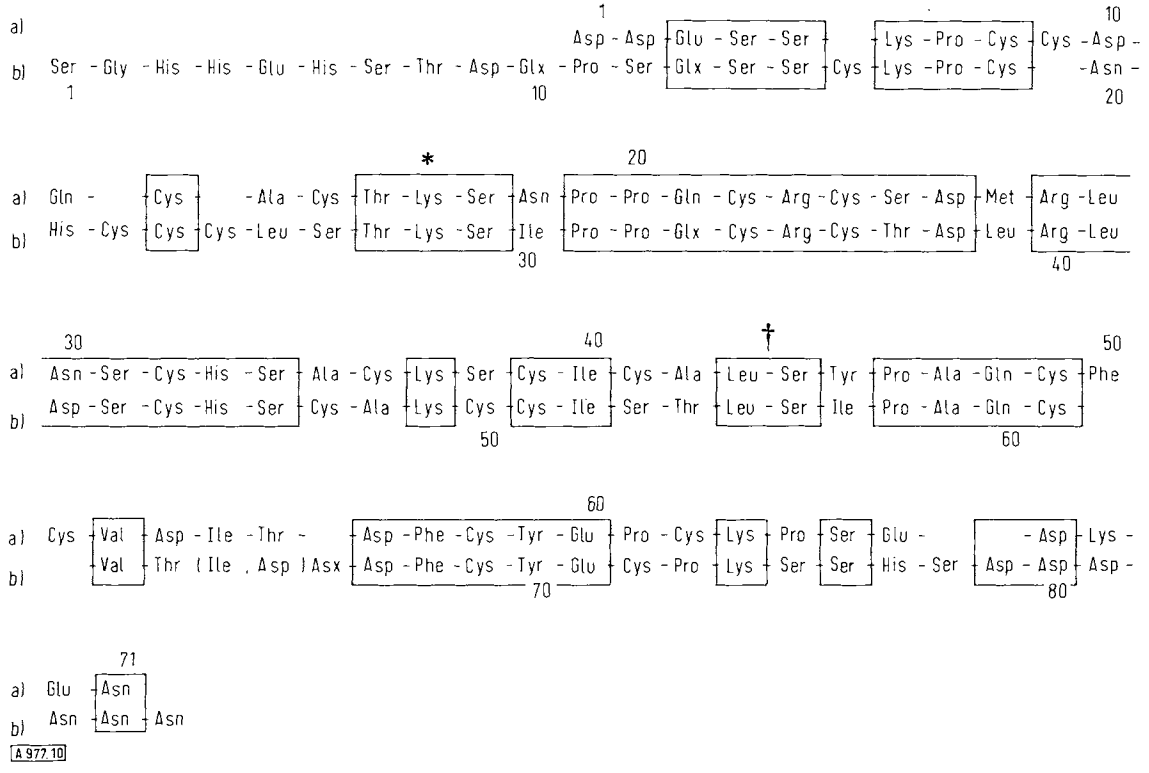


Fig. 10. Homology in the amino acid sequences of a) the soybean inhibitor (Bowman-Birk) [128] and b) the trypsin-chymotrypsin inhibitor IV from lima beans [130]. The asterisk (*) denotes the antitryptic and the cross (†) the antichymotryptic site. In the Bowman-Birk inhibitor the partial sequences Ala^{13} to Cys^{24} are homologous to Ile^{40} to Cys^{51}, in the limabean inhibitor IV the corresponding partial sequences Cys^{23} to Cys^{34} and Cys^{50} to Cys^{61}.

is found in the trypsin-chymotrypsin inhibitor from lima beans[129] (84 amino acids) (Fig. 10b). The sequence of the lima bean inhibitor was determined by *Tan* and *Stevens*[30, 130]; it has the peculiarity that it contains two homologous sequences within the single-stranded polypeptide chain, one of these sequences containing the antitryptic site and the other the antichymotryptic site[30]. On the basis of this observation, it was postulated that this "double-headed" inhibitor with two independent reactive sites sould have developed by gene duplication and divergent evolution. It is worth noting in this connection[128] that sequences similar to Lys-Ser-Asn-Pro-Pro-Gln-Cys-Arg (residues 16—23) in the Bowman-Birk soybean inhibitor (Fig. 10a) and Lys-Ser-Ile-Pro-Pro-Glx-Cys-Arg (residues 28—35) in the lima bean inhibitor (Fig. 10b) also occur in the sequence of the groundnut inhibitor (Arg-Ser-Asx-Pro-Pro-Glx-Cys-Arg) (*Hochstrasser*, *Illchmann*, and *Werle*[33, 131]), though the total sequence is otherwise quite different from that of the other two inhibitors. The assumption that these regions are particularly important to the antitryptic activity has not yet been confirmed. Similar sequences with otherwise pronounced differences are also found in the groundnut inhibitor (Ala-Pro-Pro-Tyr-Phe-Glx-Cys, residues 23—29) and in the inhibitor from corn seeds (Leu-Pro-Pro-Leu-Glx-Lys-Thr-Cys, residues 26—33), which were also investigated by *Hochstrasser*, *Illchmann*, and *Werle*[33, 132].

Due to their very different primary structures, all the trypsin inhibitors mentioned here are excellent examples of convergent protein evolution in nature.

8.2. Covalent Structures

The complete covalent structure is determined by the crosslinking of the polypeptide main chain by disulfide bridges. The three cystine residues in the trypsin-kallikrein inhibitor (Kunitz) connect postions 5 and 55, 14 and 38, and 30 and 51[116, 119] (Fig. 6a); the three cystine residues of the secretory pancreatic inhibitors (Kazal type) connect residues 9 and 38, 16 and 35, and 24 and 56[92, 133–136] (Fig. 6b), whereas the five bridges in the Ascaris inhibitor connect positions 5 and 28, 16 and 44, 19 and 58, 21 and 38, and 43 and 64[137] (Fig. 8). In the soybean inhibitor (Kunitz), residues 39 and 86 and residues 136 and 145[138] are joined by two disulfide bridges (Fig. 9). The recently determined structure of the trypsin-chymotrypsin-inhibitor (Bowman-Birk) from soybeans (double headed inhibitor, see Section 9) is held by 7 disulfide bridges, which connect the half-cystine residues 8 and 62, 9 and 24, 12 and 58, 14 and 22, 32 and 39, 36 and 51, and 41 and 49[230][*].

The biological activity of the proteinase inhibitors is destroyed on complete reduction of the disulfide bridges, but is generally recovered on mild reoxidation[19, 92, 123].

Only provisional conclusions can be drawn from the few available data on the complete covalent structures and on the position of the reactive sites. The hypothesis proposed by *Ozawa* and *Laskowski, Jr.*[88] that the reactive site peptide linkage -P_1-P'_1- is present as a "cyclic substrate" in a ring closed by a disulfide bridge ("disulfide loop") is supported by the structures of the trypsin-kallikrein inhibitor (Kunitz) (P_1-P'_1 = Lys^{15}-Ala^{16}[90]), the secretory pancreatic inhibitors (Kazal type) (P_1-P'_1 = Arg/Lys^{18}-Ile^{19}[18, 64, 92, 100]), and of the soybean inhibitor (Kunitz) (P_1-P'_1 = Arg^{63}-Ile^{64}[88]), and is probably also valid for the Ascaris inhibitor, whose reactive site has not yet been identified. The trypsin-chymotrypsin inhibitor (Bowman-Birk) contains the antitryptic and the antichymotryptic site in a disulfide loop. Both halves of the molecule could each be separated by peptic hydrolysis of the bond Asp^{56}-Phe^{57} and by cyanogen bromide cleavage of the bond Met^{27}-Arg^{28} into a (single headed, see Section 9) trypsin inhibitor and a chymotrypsin inhibitor (*Odani* and *Ikenaka*[239]). The serum inhibitors α_1-antitrypsin and α_1-antichymotrypsin[46], in which at first no cystine was detected at all, and which were regarded as exceptions, have also been shown to contain a disulfide bridge[204].

The antitryptic site in all the trypsin inhibitors whose sequences have been established is situated in the N-terminal part of the polypeptide chain, which is then closed by a disulfide bridge to form a ring. There seems to be some reason to assume that the C-terminal part is arranged parallel or antiparallel to parts of this ring, and that the rigid conformation required for the reactive site, which is also manifested in the low values of the hydrolysis constant K_{hyd}, is fixed by hydrogen bonds as in the β-structure. This type of construction could also be deduced from the covalent structure of the secretory pancreatic inhibitors and both halves of the molecule of the soybean inhibitor (Bowman-Birk), and has been detected for the trypsin-kallikrein inhibitor by X-ray structural investigations[139, 140].

8.3. Three-Dimensional Structure of the Trypsin-Kallikrein Inhibitor (Kunitz)

The three-dimensional structure of the trypsin-kallikrein inhibitor (Kunitz) was elucidated in the first X-ray crystal structural analysis of an inhibitor with a resolution of 2.5 Å by *Huber*, *Kukla*, *Rühlmann*, *Epp*, and *Formanek*[139]. The molecule is pear-shaped, with a length of 29 Å and a maximum diameter of 19 Å (Fig. 11, cf. Figs. 5a and 6a). The shape is determined by a double-stranded, antiparallel pleated sheet structure formed by the residues Ala^{16} to Gly^{36} and twisted through almost 180°. The two antiparallel strands are held together at the tip of the molecule by the disulfide bridge Cys^{14}-Cys^{38}. The segment of the residues Cys^{38} to Ser^{47} crosses the pleated sheet structure at Phe^{45}, which is connected by hydrogen bonds *via* its carbonyl oxygen and its nitrogen atom to Tyr^{21}, so that a short section of a three-stranded β structure is formed. Another hydrogen bond from the carbonyl oxygen of Thr^{11} to the nitrogen of Gly^{36} fixes the N-terminal part of the main chain in the form of a parallel pleated sheet structure. Two segments of a polyproline-II helix are formed by the residues Arg^{39} to Lys^{41} and Glu^{7} to Tyr^{10}. These segments contain the sequence Pro^{8}-Pro^{9}, which evidently favors the formation of this structure[140]. The disulfide bridge Cys^{30}-Cys^{51} binds three turns of an α-helix of the carboxyl terminus to the pleated sheet structure, while the bridge Cys^{5}-Cys^{55} fixes a distorted helical segment of the residues Asp^{3} to Glu^{7}, which does not form hydrogen bonds, close to the amino end.

The interior of the molecule is filled with hydrophobic residues, mainly phenylalanine and cystine. Nearly all the hydrophilic residues are located on the surface and are directed into

[*] A figure of this interesting structure could, unfortunately, not be added in proof.

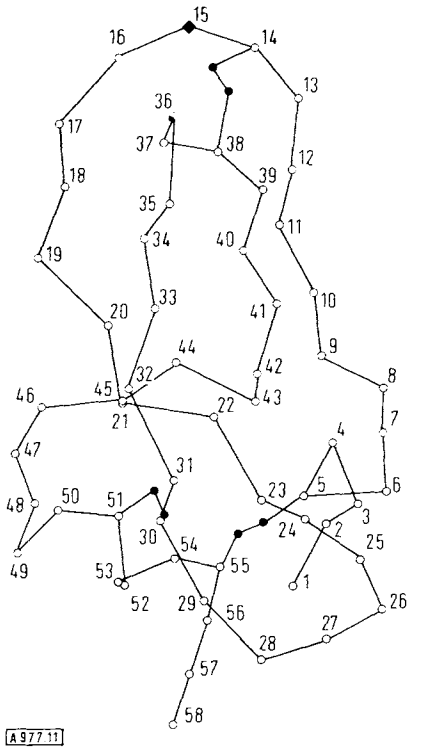


Fig. 11. Projection of the three-dimensional structural model of the trypsin-kallikrein inhibitor (Kunitz) [139]. The positions of the α-carbon atoms of the peptide chain are indicated. ● = sulfur atoms of the disulfide bridges, ● = Lys^{15}.

the surrounding solvent. All negative charges are situated at the base of the molecule, whereas the positive charges seem to be concentrated at the "tip" of the molecule, which contains the reactive site (Lys^{15}-Ala^{16}), *i.e.* the site of contact with the proteinases. The inhibitor thus has a large dipole moment, which possibly facilitates its correct orientation with respect to the proteinase[140, 141].

Very recent results obtained by *Deisenhofer* and *Steigemann*[159] at a resolution of 1.5 Å show that the peptide linkage Lys^{15}-Ala^{16} is strained. This linkage is already distorted in such a way that a tetrahedral arrangement is preformed; it is not planar anymore.

8.4. Structure of the Complex C

Initial model investigations on the three-dimensional structure of the complex C from trypsin-kallikrein inhibitor (Kunitz) and chymotrypsin have been carried out by *Blow*, *Wright*, *Kukla*, *Rühlmann*, *Steigemann*, and *Huber*[141, 142]. *Stroud*, *Kay*, and *Dickerson*[143] have considered the association of the inhibitor, with the model of the trypsin molecule.

The X-ray structure of the crystalline trypsin complex was established by *Rühlmann*, *Kukla*, *Schwager*, *Bartels*, and *Huber*[198] with a resolution of 2.8 Å. The structure found

Table 1. Hydrogen bonds between the trypsin-kallikrein inhibitor (Kunitz) and trypsin (the arrangement according to [142] based on model investigations on the inhibitor and α-chymotrypsin have been corrected according to the results of the X-ray structural analysis of the complex of the inhibitor and trypsin according to [198] and [242].

Participating amino acids (and atoms)	
Inhibitor	Enzyme
Pro^{13} (CO)	Gly^{216} (NH)
Lys^{15} (CO)	Ser^{195} (NH), Gly^{193} (NH)
Lys^{15} (NH)	Ser^{214} (CO)
Lys^{15} (ε-NH_2)	Asp^{189} (β-CO)
Ala^{16} (CO)	Gln^{192} ($CONH_2$)
Arg^{17} (NH)	Phe^{41} (CO)
Gly^{37} (CO)	Tyr^{54} (OH)

Table 2. Type and numbers of interactions between the trypsin-kallikrein inhibitor (Kunitz) and trypsin according to the X-ray data of the crystallized complex [242].

PTI / Trypsin	Thr^{11}	Gly^{12}	Pro^{13}	Cys^{14}	Lys^{15}	Ala^{16}	Arg^{17}	Ile^{18}	Val^{34}	Tyr^{35}	Gly^{36}	Gly^{37}	Cys^{38}	Arg^{39}
Tyr^{39}							V							
His^{40}							H							
Phe^{41}						V	H, V	V						
Cys^{42}						V								
His^{57}				V	V	V					V	V	V	
Cys^{58}						V								
Tyr^{59}														
Lys^{60}								V						
Ser^{96}														
Asn^{97}														H, V
Thr^{98}														V
Leu^{99}				V									V	V
Tyr^{151}							V, CT		V					
Gln^{175}														H
Asp^{189}					S									
Ser^{190}					H, V									
Cys^{191}					V									
Gln^{192}	H?	H?, V		H	V	V								
Gly^{193}					H, V	V	V							
Asp^{194}					H									
Ser^{195}				V	C?, V, H	V								
Ser^{214}					H									
Tyr^{215}			V	V	V								V	
Gly^{216}			H, V											

is extremely similar to that predicted from the structures of the components[141, 142].

The peptide linkage Lys^{15}-Ala^{16} of the inhibitor is situated at the calatytically active site of the enzyme in the complex, so that the inhibitor completely covers the surface of the enzyme and the side chain of Lys^{15} is inserted into the specificity pocket of the enzyme. Eleven[242] hydrogen bonds and more than 200 van der Waals contacts seem possible between trypsin (or chymotrypsin) and the inhibitor (Tables 1 and 2). These are all confined to the near neighborhood of the catalytically active residues Ser^{195}, His^{57}, and Asp^{102} of the enzyme[*]. Water is completely excluded from this contact region. Most of the contacts are made by the flexible side chains of the residues Lys^{15}, Ala^{16}, Arg^{17}, and Arg^{39} of the inhibitor with parts of the enzyme for which it is known that amino acid substitutions between trypsin and chymotrypsin are particularly conservative[**]. The insertion of the lysine side chain into the specificity pocket of the enzyme is favored by the possibility of ion-pair formation between the ε-amino group of Lys^{15} and the β-carboxylate group of Asp^{189}; however, chymotrypsin can also incorporate lysine, though it has Ser^{189} instead of Asp^{189}[142, 198]. It is assumed that the binding pocket of chymotrypsin also contains space for water molecules, which could help in the dispersion of the positive charge of Lys^{15}[142] (cf. Section 9).

After the formation of the loose Michaelis complex L or L* from the enzyme and the inhibitor, the formation of an acylenzyme intermediate with covalent linkage of the enzyme to the inhibitor as in normal substrate hydrolysis seems sterically possible, since the peptide linkage Lys^{15}-Ala^{16} (P_1-P'_1) is brought into contact with the catalytically active residues Ser^{195} and His^{57} in exactly the same way as that of a hydrolyzable substrate[142]. It is therefore likely that this peptide linkage P_1-P'_1 can be attacked. A reaction of this type in the inhibitor-enzyme interaction is supported by the partial proteolysis (see Section 5.2) of this peptide linkage in a series of proteinase inhibitors. The fundamental question of the molecular structure of the complex C has been provisionally answered through the X-ray structural analysis of the complex of trypsin with trypsin-kallikrein inhibitor (Kunitz)[198].

This complex is an adduct with a tetrahedral intermediate state, a situation approaching a covalent bond between the enzyme and the inhibitor and a geometry of the Lys-Ala peptide bond between tetrahedral coordination at the carbonyl carbon and planar configuration. Stabilization purely by secondary valence interactions or an acylenzyme complex structure had formerly been under discussion as alternatives. According to *Birktoft* and *Blow*[199] and *Henderson*[144], native chymotrypsin and acylated chymotrypsin differ in the position of the β-oxygen of Ser^{195}, which is turned through 120° about the C_α—C_β axis into a "bonded" position in the acyl derivative. A "bonded" position of this atom, corresponding to a situation of covalent bond between it and the carbonyl carbon of Lys^{15} (P_1) of the inhibitor, is clearly shown by the X-ray structural analysis of the complex. The covalent peptide linkage between residues P_1-P'_1 (Lys^{15}-Ala^{16}) (I)[***] is still present in the complex[198]. The mean value of the distance between the β oxygen of Ser^{195} to the carbonyl carbon of Lys^{15} is about 2.3 Å and, therefore, is longer than that of a covalent bond. However, it favors a strong interaction of the serine nucleophile with the electrophilic center, the carbonyl carbon of Lys^{15}. The tetrahedral arrangement is stabilized by the hydrogen bond between $N^{\varepsilon 2}$ of His^{57} (E) and the hydroxyl group of Ser^{195}[198]. This structural characteristic is in agreement with the transfer of the hydroxyl proton of Ser^{195} to His^{57} on formation of the tetrahedral adduct[201]. The position of $N^{\varepsilon 2}$ of His^{57} in the complex allows the rotation of the β-oxygen of Ser^{195} from the "native position" into the "bonded acyl position" without a change of more than 0.3 Å in the O—N contact distance. The hydrogen bond is thus retained *via* the covalently bonded oxygen, as a strong proton acceptor, but the energy of the transition state of the reaction leading to the complex C is reduced (Fig. 12)[198].

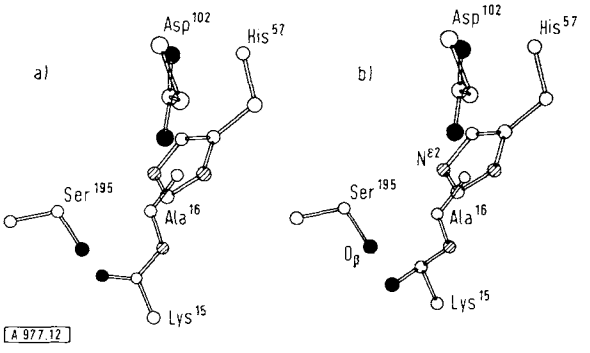


Fig. 12. Comparison of the atomic arrangements of the catalytically active residues Asp^{102}, His^{57}, and Ser^{195} of trypsin (for numbering, see footnote in Section 7) and of the residues of Lys^{15}-Ala^{16} (P_1-P'_1) of the reactive site of the trypsin-kallikrein inhibitor (Kunitz) in the complex. a) Hypothetical arrangement in the model of a complex of trypsin and native, unmodified inhibitor, b) arrangement found from the X-ray crystal structural analysis [198] with tetrahedrally coordinated carbonyl carbon of Lys^{15} in the inhibitor. ○ = C, ● = O, ⊘ = N.

The distance of 4.1 Å between the amide nitrogen of the "substrate leaving group" of Ala^{16} (I) and $N^{\varepsilon 2}$ of His^{57} (E), as well as the unsuitable orientation of the imidazole ring, prevents the direct proton transfer[145] and hence the formation of the acylenzyme intermediate[198, 242]. A structural reorientation of the imidazole ring with rotation about the C_α—C_β and C_β—C_γ axes would be necessary in order to bring the ε2-nitrogen closer to the amide nitrogen of Ala^{16} (I). This necessitates weakening of the hydrogen bonds between the β-oxygen of Ser^{195} (E) and $N^{\varepsilon 2}$ of His^{57} and between $N^{\delta 1}$ of His^{57} and the β-carbonyl oxygen of Asp^{102} (E)[198].

The tetrahedral structure of the complex is stabilized by two further hydrogen bonds between the enzyme and the inhibitor (see Table 1) and the hydrogen bond from the amide nitrogen of Ala^{16} (I) to the carbonyl oxygen of Gly^{36} (I). The latter hydrogen bond belongs to the twisted pleated sheet structure of the inhibitor[139] (see Section 8.3).

The inhibitor chain of Tyr^{35} to Cys^{38} and the space-filling disulfide bridge Cys^{14}-Cys^{38} completely exclude water from the contact site on the surface of the enzyme, and thus stabilize the hydrogen bonds. On formation of the acylenzyme intermediate with cleavage of the peptide linkage between Ala and Lys, the hydrogen bond from the amide nitrogen and a number of hydrophobic contacts of Ala^{16} (I) must obviously be weak-

[*] See footnote in Section 7.

[**] "Conservative" here means that the character of the amino acid (hydrophilic, hydrophobic) is unchanged or that no substitutions due to mutation occur.

[***] E = enzyme, I = inhibitor.

ened. Normal substrates of the enzyme, on the other hand, have a less rigid structure, and the flexibility of the polypeptide chain allows the access of water to the imidazole ring of His^{57}. The amide nitrogen of the leaving group is protonated, with formation of the acylenzyme intermediate.

The final fine-structure analysis of the inhibitor[159] will show the extent to which deformation of the reactive site peptide linkage P_1-P'_1 (Lys^{15}-Ala^{16}) toward the tetrahedral arrangement in the complex sterically favors the formation of the adduct[198].

The molecular structure of this tetrahedral complex already offers an explanation for the differences in the reaction rate constants $k_{-2} > k_3$ observed for the soybean inhibitor (Kunitz) (see Section 6.2). The protonation of the amide nitrogen of the leaving group (P'_1) calls for a change in the conformation of His^{57} of the enzyme before the proton transfer[159, 198].

Many objections have been raised against the general validity of the model with covalent linkage of the enzyme and the inhibitor in the stable complex C (tetrahedral complex or acylenzyme complex). *Feinstein* and *Feeney*[146, 147] have reported observations on the association of inhibitors with catalytically inactive enzymes. *Foster* and *Ryan*[148] observed complex formation between anhydrochymotrypsin and the chymotrypsin inhibitor from potatoes, and *Dlouha* and *Keil*[149] have observed complex formation between bovine trypsinogen and the trypsin-kallikrein inhibitor (Kunitz) (for a discussion see Ref. [19]).

The X-ray structural analysis recently carried out by *Sweet, Janin*, and *Blow*[200] on the crystalline complex of pig trypsin with soybean inhibitor (Kunitz) also showed tetrahedral coordination of the carbonyl carbon for the molecular structure of the complex C at the reactive site. Thus, the same intermediate state was found here as for the complex of trypsin with trypsin-kallikrein inhibitor (Kunitz).

The model discussed and verified by the X-ray structural analysis for the stable complex C, with an interatomic distance corresponding to a covalent linkage between the enzyme and the inhibitor, corresponds to the suggestion of *Finkenstadt* and *Laskowski, Jr.*[18, 150] for the "central" intermediate C. It is in agreement with the kinetic data and the symmetry of the observed enzymatic catalytic processes of the enzyme-inhibitor association of the soybean inhibitor (Kunitz), and explains the phenomenon of the partial proteolysis reaction. In view of the structural similarity of the serine proteinases, it is very probable that many other enzyme-inhibitor complexes are constructed according to the same principle. It still remains to be shown, however, whether a complex having the particular structure of a tetrahedral adduct has a more favorable association energy than a complex that is stabilized by pure secondary-valence interactions.

9. Specificity

The inhibition specificity of inhibitors for proteinases having different proteolytic specificities is important to their physiological function. It can vary considerably over a wide range. A large number of data have been assembled in the literature[12-24], but these data are not always reliable, owing to defective methods or impure materials. Moreover, the constants for the association of different enzymes with the same inhibitor can differ by several orders of magnitude, and consequently cannot always be determined under comparable experimental conditions.

The broad variation in inhibitory specificities is a consequence of the molecular protein interactions between enzyme and inhibitor, a detailed understanding of which is only now beginning through the combination of sequence data and X-ray structural data.

Two enzymes can be inhibited cooperatively, competitively, or independently by one inhibitor molecule[19]. No examples of cooperative inhibition are known as yet. Competitive inhibition can take place *via*: 1. the same reactive site (single-headed inhibitor), 2. several overlapping reactive sites (multi-headed inhibitor), and 3. several non-overlapping reactive sites ("multi-headed" inhibitor).

Only a few examples of the first type have been investigated in detail. The identity of the antitryptic site and of the antichymotryptic site of soybean inhibitor (Kunitz) has been conclusively demonstrated by *Bidlingmeyer, Leary*, and *Laskowski, Jr.*[96]. The same site is also responsible for the inhibition of cocoonase, the trypsin-like enzyme of the silkworm[19].

According to *Fritz, Schiessler, Brey, Tschesche*, and *Fink*[151], the secretory inhibitors of the mammalian pancreas, which have previously been regarded as very trypsin-specific, also inhibit the proteinase acrosin from boar sperm and from human sperm[152] and a pancreatic proteinase that converts proinsulin into insulin[153]. Initial findings point to the presence of the same reactive site in this and other "single-headed" inhibitors. Out of the series of structurally similar serine proteinases with comparable specificities, such as trypsin, plasmin, thrombin, urokinase, cocoonase, acrosin, and pancreatic kallikrein[154], "single-headed" inhibitors inhibit only certain enzymes, depending on their specificity, and the affinities also differ very considerably in some cases. We found that different isoinhibitors from the edible snail inhibit trypsin with the same association constant, but differ very considerably in the inhibition of pancreatic kallikrein[214]. A still more pronounced selectivity was found for the isoinhibitors of the cuttlefish, all of which inhibit trypsin, chymotrypsin, and pancreatic kallikrein, but not plasmin[38].

The selectivity can even become more pronounced within a class of homologous inhibitors, and can change into species specificity. Thus the secretory pancreatic inhibitors (Kazal type) of cattle and of pigs have the same sequence regions in the reactive site apart from the Arg↔Lys mutation of the residue P_1 (see Section 8.1); they both inhibit pig and bovine trypsins, but they do not measurably inhibit human trypsin[155]. On the other hand, the human trypsin inhibitor inhibits not only human trypsin I and II[156] but also bovine trypsin[157]. Despite this difference in species specificity, extensive homology of these pancreatic inhibitors must be expected on the basis of evolutionary relationship. Sequence comparisons within this class are therefore of special interest.

In the second case, where there are several overlapping reactive sites, extensive molecular studies are necessary, since no definite conclusion can be drawn from competitive inhibition experiments. Independent and overlapping reactive sites for trypsin and chymotrypsin have also been discussed on the basis of changed specificities of chemically modified trypsin-kallikrein inhibitor (Kunitz)[113, 158], as has a single site for

both enzymes (first case, see also Section 8.3). *Sevilla* and *Righi*[95, 160] found that the antitryptic activity of the trypsin-kallikrein inhibitor (Kunitz) disappears on acetylation, whereas the antichymotryptic activity is only reduced. The presence of two independent, but overlapping reactive sites (double-headed) is concluded from this evidence. Another possible example is the trypsin-chymotrypsin inhibitor from Japanese radish seeds[161]. The resynthesis of the peptide bond (between Lys^{15} and Ala^{16}) in the "synthetic" modified trypsin-kallikrein inhibitor (Kunitz) by trypsin[213] *and* chymotrypsin[231] (see Section 5.2) has, in our opinion, conclusively demonstrated the identity of both reactive sites (single headed). The third case, *i.e.* the presence of independent non-overlapping sites, has been found for the inhibition of trypsin and chymotrypsin by the inhibitors from soybeans (Bowman-Birk)[74, 162], lima beans[30, 163, 164], and other beans[19, 165, 166] and for the canine submandibular inhibitor[202] and the ovoinhibitor from hens' egg-white[167] and several bird ovomucoids[168].

The "double-headed" trypsin-chymotrypsin inhibitor (Bowman-Birk) has been converted into a "single-headed" chymotrypsin inhibitor by cleavage of the peptide bond in the trypsin-specific site and subsequent removal of the reactive lysine residue by carboxypeptidase B[162]. In the Lima bean inhibitor, whose single-stranded polypeptide chain has two homologous regions (Fig. 10b), the antitryptic site (Lys^{28}-Ser^{29}) was found in the N-terminal region. The antichymotryptic site (Leu^{55}-Ser^{56}) is situated in the corresponding position in the homologous C-terminal region[30]. The different specificities of two homologous regions with only two other conservative point mutations seem to be entirely due to the amino acid substitution lysine↔serine, which calls for a double base change in the genetic code.

The ovoinhibitor from hens' egg-white, a glycoprotein with only one polypeptide chain (MW 49000), binds two moles of trypsin and two moles of chymotrypsin separately and independently of one another[167], and can therefore be described as "multi-headed"[168].

The inhibitors of blood plasma mostly also have broad specificities, and in addition to trypsin or chymotrypsin, some of them also inhibit plasmin, pancreatic kallikrein, thrombin, C1-esterase, or elastase[46]. It has not yet been established whether they have several reactive sites or only one. The independent inhibition of two moles of trypsin has been observed for α_2-macroglobulin[169]. However, this very high molecular weight protein has been shown to be built up from subunits[226], and an abnormal inhibition mechanism is also probable, since trypsin, plasmin, and thrombin can hydrolyze low molecular weight substrates even in the complex with α_2-macroglobulin[170].

10. Temporary Inhibition

In addition to hen ovomucoid[75] and all the mammalian secretory pancreatic inhibitors (Kazal type) investigated so far[42, 43, 65, 76, 171] (see Section 4.2), the temporary inhibitors for trypsin also include the seminal inhibitors from guinea pig seminal vesicles[48] and from boar sperm[172] (cf. below). The trypsin-kallikrein inhibitor (Kunitz) from bovine organs also becomes a temporary inhibitor for trypsin on reduction of the disulfide bridge Cys^{14}-Cys^{38}, though the native inhibitor exhibits permanent inhibition and is completely resistant to more than 20 proteolytic enzymes[173, 174].

Two alternative mechanisms have been discussed for the proteolytic inactivation of the inhibitors during temporary inhibition. *Laskowski, Sr.* and *Wu*[76], on the basis of the change in the rate of inactivation on addition of excess inhibitor (and of excess trypsin) to the complex, postulated an attack by free trypsin on the inhibitor bound in the complex. *Tschesche* and *Klein*[65] found that the proteolytic degradation of the pancreatic secretory inhibitor to form modified and inactive products occurs both in solution (with dissolved trypsin) and on insoluble trypsin resin used for complex formation. On steric grounds, therefore, they favored degradation from the associate L or L* with simple reorientation of the enzyme molecule. This view is supported by the observation of the progressive degradation of the inhibitor even under completely unphysiological conditions in the pH range from 2.5 to 10 and with less than the equimolar quantity of trypsin; in this case, no trypsin activity toward natural or synthetic substrates can first be detected[65]. The maximum modification and inactivation occurs at pH = 3.4[65, 78]. *Laskowski, Sr. et al.*[77] were able to show that the complete reliberation of the trypsin from a mixture of excess inhibitor and trypsin that had been incubated at pH = 3.4 until 20% of the initial activity was present ultimately proceeds more rapidly after neutralization to pH = 8.0 than when the incubation is continued in acidic solution. This observation justified the conclusion that the inactivating cleavage occurs after the modifying proteolysis in the reactive site (pH optimum at pH < 7), and that the pH optimum for the inactivating cleavage is around pH = 8.0, *i.e.* at the normal pH optimum for tryptic activity.

By correlation of the inactivation with the cleavage of individual peptide linkages of the inhibitor, we were able to demonstrate the correctness of this hypothesis for the inhibitor I of pigs[175]. Corresponding results were obtained by *Schneider* and *Laskowski, Sr.*[205] for the inhibitor II of pigs. After the modifying cleavage of the peptide linkage P_1-P'_1 at the reactive site, after which the inhibitor is still active, the molecule is inactivated by proteolysis of the peptide linkage Arg^{44}-Gln^{45} (Fig. 13). Selective chemical blockage of this bond against cleavage with trypsin by modification of the Arg^{44} side chain with butanedione consequently retards the degradation in

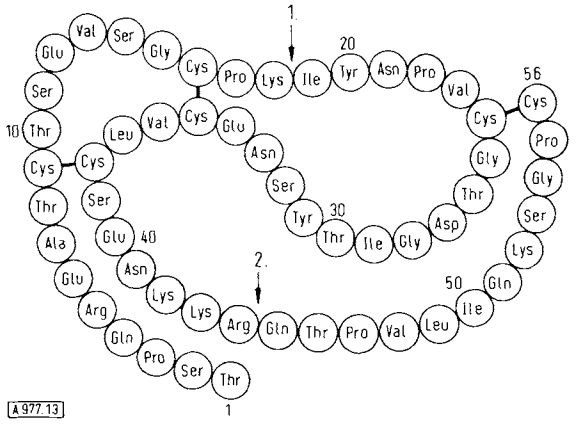


Fig. 13. Complete covalent structure of the secretory trypsin inhibitor I from pig pancreas with reactive site (first cleavage site in the partial proteolysis) and "nominal point of rupture" for inactivation (second cleavage site in the partial proteolysis) during temporary inhibition (see also Fig. 7a).

the temporary inhibition[175]. Finally, the bonds Lys^{52}-Ser^{53} and Lys^{42}-Lys^{43} are hydrolyzed on proteolysis[175, 205].

Thus, the peptide linkage Arg^{44}-Gln^{45} could be regarded as the nominal point of rupture of the molecule. Cleavage at this linkage by reorientation of the enzyme molecule trypsin is energetically not very favorable, owing to the high association constant at the reactive site. However, since it inactivates the molecule, one must expect a steady displacement of the equilibrium until inactivation is complete.

Because of the proteolytic degradation of the inhibitor by the enzyme, this property of temporary inhibition depends on the specificity of the enzyme. We found[203] that the seminal inhibitor from boar sperm, which inhibits the enzymes trypsin, plasmin, and acrosin, acts as a temporary inhibitor toward trypsin, but inhibits the sperm enzyme acrosin permanently[172].

11. Physiological Function

The physiological function of many proteinase inhibitors has not yet been explained. This is true in particular of all inhibitors from plants. It has been suggested that their function is concerned with the interruption of proteolytic processes in the resting stage of the seeds[176], while another view is that they "generally play a part in the maintenance of the latent life form by inhibition of autolysis"[177]. In the case of plants that live symbiotically with bacteria (*e.g.* Leguminosae), the protection of plant tissue against the bacterial proteinases at the point of colonization and a protective function against overgrowth by the bacteria have also been discussed[8].

Green and *Ryan*[216] recorded a very pronounced increase in the proteinase inhibitor concentration in all the leaves of potatoes and tomatoes as a result of damage to single leaves by insects. This effect can also be produced by mechanical injury, and is due to the release of a "wound hormone" (PIIF, proteinase inhibitor inducing factor) at the site of the injury[217].

The physiological function of the secretory pancreatic inhibitors, which occur in all mammals, is very probably the prevention of premature zymogen activation of the digestive enzymes by inhibition of the activating key enzyme trypsin (in cases of premature trypsinogen activation) in the duct system and in the storage sites (acinar cells) of the glands. The trypsinogen is then activated in the duodenal tract by enterokinase. This view is strongly supported by the simultaneous and parallel secretion of the pancreatic inhibitors with the zymogens[42, 43], as well as by the limited specificity of these inhibitors and the fact that they inhibit temporarily. The latter property allows the recovery of the inhibited trypsin after secretion into the duodenal tract for the digestive function.

On the other hand, the function of the trypsin-kallikrein inhibitor (Kunitz) that occurs in tissue can hardly be concerned with the basic biochemical processes, since it does not occur in all mammals and it appears in the tissues only after birth[178]. Its function has been correlated with the special position of ruminants[8], where a special metabolism by the gastrointestinal fauna must be taken into account. The homologous colostrum inhibitor (see Sections 2 and 8.1), which appears to be secreted by all mammals[179], may have the function of protecting the immune bodies of the mother[180] against enzymatic degradation during their passage through the small intestine and allowing their undegraded reabsorption[179].

The snail inhibitors[36, 63], which have a broader inhibition spectrum than the trypsin-kallikrein inhibitor (Kunitz), are secreted into the snail's slime[36], and could therefore function as protection against the proteinases of the snail's natural biotope. In the case of the Ascaris inhibitors, the protective function against the digestive enzymes of the host organisms is obvious[3, 72]. However, objections against a simple "defense mechanism" have been put forward[243] and the inhibitors have been viewed as part of a macromolecular transport system that is necessary for the worm to stay alive[243].

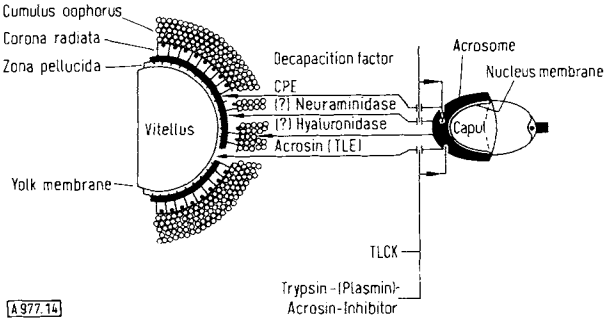


Fig. 14. Schematic representation of ovum and sperm with the penetration enzymes of the acrosome and their inhibitors [184]. Cumulus oophorus = granulosa cells; CPE = corona penetrating enzyme, TLCK = irreversible acrosin inhibitor, 7-amino-1-chloro-3-tosylamino-2-heptanone ($N\alpha$-tosyl-L-lysyl chloromethyl ketone).

Inhibition of acrosin *in vitro* and *in vivo*[47, 48, 181, 182, 184] has been conclusively demonstrated by the inhibitors of mammalian sperm and sperm plasma. Acrosin, the trypsin-like enzyme from the acrosomal cap at the head of the spermatozoon, is responsible for the penetration of the egg-cell membrane (zona pellucida), and together with the "corona penetrating enzyme" and hyaluronidase and neuraminidase[183, 186], it is the key enzyme for the fertilization process (Fig. 14). The acrosin activity is high in epididymal spermatozoons (storage form) and is absent in ejaculated spermatozoons that have come into contact with the secretion of the seminal vesicles. However, it reappears in "capacitated" spermatozoons that have spent some time in the female genital tract. It is only through this process of "capacitation" that the spermatozoons acquire their ability to fertilize the ovum. *Zaneveld, Polakoski, Robertson,* and *Williams*[47, 182, 185] and *Stambaugh* and *Buckley*[183] have shown that capacitated spermatozoons are decapacitated again by *in-vitro* treatment with seminal inhibitors of the seminal vesicles, and the fertilization of the ovum can be prevented in this way *in vivo*. These findings open up possibilities for antienzymatic contraception with proteinase inhibitors.

The spermatozoons, with their lysosomal enzymes, introduce a considerable potential of proteolytic enzymes in the female genital tract, these enzymes being inhibited by the secretion of the seminal vesicles (seminal plasma). It is not yet certain whether this merely provides protection for the female mucosal epithelium or whether there is an unknown physiological function in connection with capacitation. The hormonal regulation of sperm plasma inhibitors in the seminal vesicles, the sites of their biosynthesis, is known[187] (Fig. 15).

The concentrations of the trypsin and chymotrypsin inhibitors of blood plasma are also subject to hormonal control[188].

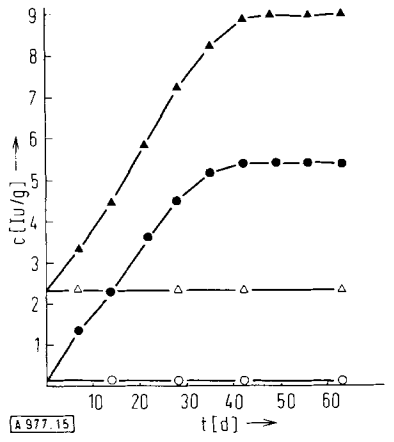


Fig. 15. Inhibitor concentration c in the seminal vesicles of mice [187]. Normal: (○ – ○), 30 days after castration: (○ – ○) and after stimulation of the normal (▲ – ▲) and of the castrated mice (● – ●) with testosterone. 1 IU inhibits approx. 1 mg of trypsin.

The inhibitor concentration in mice and rats increases significantly from birth to maturity[189]. However, the physiological and pathophysiological function of the serum inhibitors is still largely unknown.

Inhibitors may also play a part in the control of the concentrations of some polypeptide hormones in the blood stream. As was first shown by *Tschesche*, *Kolb*, *Standl*, and *Diete*[219] in human beings and by *Tschesche* and *Brush*[220] in rats, an insulin-degrading sulfhydryl enzyme can be inhibited *in vitro* by proteinase inhibitors, and the degradation can be retarded in this way. An inhibitor for the insulin-specific proteinase of rats has been detected in human serum by *Brush*[221].

The observation by *Schumacher*[190] that serum inhibitors, particularly α_1-antitrypsin, occur in the cervical mucus of women and that their concentration depends on the menstrual cycle and is extremely low one to two days before ovulation[190] (Fig. 16) is related to the biochemical processes involved in fertilization. In addition to these inhibitors, it is possible that a low molecular weight trypsin-chymotrypsin inhibitor is also present in the cervical secretion of women[206]. Acrosin is also inhibited by serum inhibitors (α-antitrypsin and antithrombin III as progressive inhibitors[191] and inter-α-trypsin

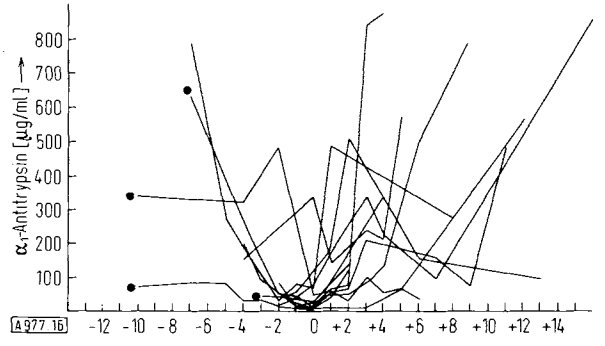


Fig. 16. Content of α_1-antitrypsin in human cervical mucus in the course of 12 menstrual cycles. For ease of comparison, the day of ovulation (the last day of the low basal temperature) was chosen as zero on the abscissa [190]. ● : ovulation induced by gonadotropins.

inhibitor with immediate action[191,207]). Sufficient ovoinhibitors or ovomucoids are available for the inhibition of the sperm proteinases after the penetration of the spermatozoon into the ovum. It has been shown that boar acrosin is inhibited by ovomucoid from hen's egg white[47,192] and by the inhibitor from the nidamental gland of the cuttlefish[193]. *Feeney*[35] has described the inhibition of the acrosin-like pancreatic enzyme trypsin by many ovoinhibitors and ovomucoids from poultry eggs.

The plasma inhibitors from the sera of warm-blooded (and cold-blooded) animals probably have many control and regulatory functions. It is well known that many clinical pictures are accompanied by concentration changes in the α_1-globulin fraction, which consists mainly of α_1-antienzymes (α_1-antitrypsin, α_1-antichymotrypsin, and α_1-antiplasmin) and which constitutes 90% of the trypsin-inhibiting capacity of human serum[8][*]. A greatly increased susceptibility to pulmonary emphysema has been observed in homozygotes with α_1-antitrypsin deficiency of genetic origin[194], and angioneurotic edema is also attributed to a considerable deficiency of complement esterase inhibitor. Proteinase inhibitors also appear to inhibit selectively the growth of transformed cells, whereas normal cells are influenced less strongly if at all. This could offer new approaches for the treatment of malignant cells[218].

12. Outlook

The principle of temporary and local limitations of enzyme activities by inhibitors of a protein nature has been found not only in endo-proteinases of the serine hydrolase type. Inhibitors for exopeptidases, such as carboxypeptidase A and B[195], lipase[196], phospholipase[197], amylase[222], ribonuclease, and deoxyribonuclease[223] have recently also been isolated. It must therefore be expected that further inhibitors for important metabolic enzymes will also be discovered. A third possibility for the control of enzyme activities in the body must therefore be considered alongside the principles of biological regulation already known:

1. repression (or activation) of the genetically controlled protein synthesis at the DNA transcription stage,
2. inhibition (or activation) of allosteric enzymes by effectors of the intermediate metabolism (including interconvertible enzymes), and
3. inhibition (temporary, permanent, progressive) of enzymes that are already present by specific inhibitors.

The investigation of the specific enzyme-inhibitor interaction and its physiological and pathological aspects for medicinal molecular biology and applied therapy is still in its infancy. However, proteinase inhibitors are already on the market as medical supplies and have found wide therapeutre application[249].

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[*] The designations antitrypsin and antichymotrypsin for these proteinase inhibitors is a misnomer, since these pancreatic enzymes will be inhibited but do not occur in serum.

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Translated by Express Translation Service, London

[1] *C. Fermi* and *L. Pernossi*, Z. Hyg. Infektionskr. *18*, 83 (1894).

[2] Compilation by *N. Heimburger, H. Haupt*, and *H. G. Schwick* in [24].

[3] *E. Weinland*, Z. Biol. *44*, 1 (1903).

[4] *M. Kunitz* and *J. H. Northrop*, J. Gen. Physiol. *19*, 991 (1936).

[5] *M. Kunitz*, Science *101*, 668 (1945).

[6] *M. Kunitz*, J. Gen. Physiol. *29*, 149 (1946).

[7] *M. Kunitz*, J. Gen. Physiol. *30*, 311 (1947).

[8] *R. Vogel, I. Trautschold*, and *E. Werle*: Natural Proteinase Inhibitors. Academic Press, New York 1968.

[9] *E. M. Weyer*, Ann. N. Y. Acad. Sci. *146*, 361 (1968).

[10] *R. F. Steiner* and *V. Frattali*, J. Agr. Food Chem. *17*, 513 (1969).

[11] *A. Puztai*, Nutr. Abstr. Rev. *37*, 1 (1967).

[12] *I. E. Liener* and *L. M. Kakade* in *I. E. Liener*: Toxic Constituents of Plant Foodstuffs. Academic Press, New York 1969, p. 7.

[13] *M. Laskowski* and *M. Laskowski, Jr.* in *M. L. Anson, K. Bailey*, and *J. T. Edsall*: Advances in Protein Chemistry. Academic Press, New York 1954, Vol. 9, p. 203.

[14] *M. Laskowski, Sr.* in *S. P. Colowick* and *N. O. Kaplan*: Methods in Enzymology. Academic Press, New York 1955, Vol. 2, p. 36.

[15] *N. M. Green* and *H. Neurath* in *H. Neurath* and *K. Bailey*: The Proteins. Academic Press, New York 1954, Vol. 2B, p. 1057.

[16] *P. Desnuelle* in *P. D. Boyer, H. Lardy*, and *K. Myrbäck*: The Enzymes. Academic Press, New York 1960, Vol. 4, p. 128.

[17] *R. E. Feeney* and *R. G. Allison*: Evolutionary Biochemistry of Proteins. Wiley, New York 1969.

[18] *M. Laskowski, Jr.* in *P. Denuelle, H. Neurath*, and *M. Ottesen*: Structure-Function Relationships of Proteolytic Enzymes. Munksgaard, Copenhagen 1970, p. 89.

[19] *M. Laskowski, Jr.* and *R. W. Sealock* in *P. D. Boyer*: The Enzymes. Academic Press, New York 1971, Vol. 3, p. 375.

[20] *S. P. Colowick* and *N. O. Kaplan*: Methods in Enzymology. Academic Press, New York 1970, Vol. 19.

[21] *B. Kassell* in [20], p. 839; *C. A. Ryan* and *B. Kassell, ibid.* p. 883.

[22] *P. J. Burck* in [20], p. 906; *F. C. Monkhouse, ibid.* p. 915.

[23] *F. Markwardt* in [20], p. 924.

[24] *H. Fritz* and *H. Tschesche*: Proceedings of the International Research Conference on Proteinase Inhibitors. de Gruyter, Berlin 1971.

[25] *K. Shimada* and *K. Matsushima*, Agr. Biol. Chem. *33*, 544, 549 (1969).

[26] *H. Umezawa* in *H. Umezawa*: Enzyme Inhibitors of Microbial Origin. University Park Press, Baltimore 1972; *N. T. L. Torstensson*, Arch. Microbiol., in press.

[27] *H. Van Vunakis* and *R. M. Herriott*, Biochim. Biophys. Acta *22*, 537 (1956).

[28] *T. Astrup, U. Nissen*, and *J. Rasmussen*, Biochim. Biophys. Acta *113*, 634 (1966).

[29] *M. Rigbi* and *M. Sela*, Biochemistry *3*, 629 (1964).

[30] *F. C. Stevens* in [24], p. 149.

[31] *K. Hochstrasser, E. Werle, R. Siegelmann*, and *S. Schwarz*, Hoppe-Seylers Z. Physiol. Chem. *350*, 249 (1969).

[32] *K. Hochstrasser, E. Werle, R. Siegelmann*, and *S. Schwarz*, Hoppe-Seylers Z. Physiol. Chem. *350*, 897 (1969); *H. D. Belitz, K. P. Kaiser*, and *K. Santarius*, Biochem. Biophys. Res. Commun. *42*, 420 (1971).

[33] *K. Hochstrasser* and *E. Werle* in [24], p. 169.

[34] *C. A. Ryan* and *L. K. Shumway* in [24], p. 175.

[35] *R. E. Feeney* in [24], p. 189.

[36] *H. Tschesche* and *Th. Dietl*, Hoppe-Seylers Z. Physiol. Chem. *353*, 1189 (1972).

[37] *G. Uhlenbruck, I. Sprenger*, and *I. Ishiyama*, Z. Klin. Chem. Klin. Biochem. *9*, 361 (1971); *G. Uhlenbruck, G. Sprenger*, and *G. Hermann, ibid.* *9*, 494 (1971).

[38] *H. Tschesche* and *A. v. Rücker*, Hoppe-Seylers Z. Physiol. Chem., in press.

[39] *H. Kraut, E. K. Frey*, and *E. Werle*, Hoppe-Seylers Z. Physiol. Chem. *192*, 1 (1930).

[40] *L. A. Kazal, D. S. Spicer*, and *R. A. Brahinsky*, J. Amer. Chem. Soc. *70*, 3034 (1948).

[41] *H. Fritz, F. Woitinas*, and *E. Werle*, Hoppe-Seylers Z. Physiol. Chem. *345*, 168 (1966).

[42] *L. J. Greene, M. Rigbi*, and *D. S. Fackre*, J. Biol. Chem. *241*, 5610 (1966).

[43] *H. Fritz, I. Hüller, M. Wiedemann*, and *E. Werle*, Hoppe-Seylers Z. Physiol. Chem. *348*, 405 (1967).

[44] *L. J. Greene, J. J. DiCarlo, A. J. Sussman*, and *D. C. Bartelt*, J. Biol. Chem. *243*, 1804 (1968).

[45] *H. Tschesche, E. Wachter, S. Kupfer*, and *K. Niedermeier*, Hoppe-Seylers Z. Physiol. Chem. *350*, 1247 (1969).

[46] *N. Heimburger, H. Haupt*, and *H. G. Schwick* in [24], p. 1.

[47] *L. J. D. Zaneveld, K. L. Polakoski, R. T. Robertson*, and *W. L. Williams* in [24], p. 236.

[48] *E. Fink, G. Klein, F. Hammer, G. Müller-Bardorff*, and *H. Fritz* in ref. [24], p. 225.

[49] *H. Tschesche* and *Th. Dietl* in: Protides of the Biological Fluids. Pergamon Press, London 1973, Vol. 20, p. 1021.

[50] *D. Čechová, V. Jonáková*, and *F. Šorm* in [24], p. 105.

[51] *H. U. Bergmeyer*: Methoden der enzymatischen Analyse. Verlag Chemie, Weinheim 1970, Vol. 1.

[52] *F. J. Kezdy* and *E. T. Kaiser* in [20], p. 3.

[53] *T. Chase, Jr.* and *E. Shaw* in [20], p. 20.

[54] *H. D. Orth* and *W. Brümmer*, Angew. Chem. *84*, 319 (1972); Angew. Chem. internat. Edit. *11*, 249 (1972).

[55] *H. Fritz, H. Schult, M. Neudecker*, and *E. Werle*, Angew. Chem. *78*, 775 (1966); Angew. Chem. internat. Edit. *5*, 735 (1966).

[56] *H. Fritz, K. Hochstrasser, E. Werle, B. Brey*, and *M. Gebhardt*, Z. Anal. Chem. *243*, 452 (1968).

[57] *H. Fritz, H. Schult, M. Hutzel, M. Wiedemann*, and *E. Werle*, Hoppe-Seylers Z. Physiol. Chem. *348*, 308 (1967).

[58] *H. Fritz, M. Gebhardt, E. Fink, W. Schramm*, and *E. Werle*, Hoppe-Seylers Z. Physiol. Chem. *350*, 129 (1969).

[59] *H. Fritz, B. Brey, M. Müller*, and *M. Gebhardt* in [24], p. 28.

[60] *K. Hochstrasser, M. Muss*, and *E. Werle*, Hoppe-Seylers Z. Physiol. Chem. *348*, 1337 (1967).

[61] *E. Fink, E. Jaumann, H. Fritz, H. Ingrisch*, and *E. Werle*, Hoppe-Seylers Z. Physiol. Chem. *352*, 1591 (1971).

[62] *H. Fritz, B. Brey*, and *L. Beress*, Hoppe-Seylers Z. Physiol. Chem. *353*, 19 (1972).

[63] *H. Tschesche* and *Th. Dietl*, Eur. J. Biochem. *30*, 560 (1972).

[64] *H. Tschesche*, Hoppe-Seylers Z. Physiol. Chem. *348*, 1216, 1653 (1967).

[65] *H. Tschesche* and *H. Klein*, Hoppe-Seylers Z. Physiol. Chem. *349*, 1645 (1968).

[66] *H. Tschesche, E. Wachter*, and *G. Kallup*, Hoppe-Seylers Z. Physiol. Chem. *350*, 1662 (1969).

[67] *N. M. Green*, J. Biol. Chem. *205*, 535 (1953); *N. M. Green*, and *E. Work*, Biochem. J. *54*, 347 (1953).

[68] *S. A. Bernhard* and *H. Gutfreund*, Proc. Nat. Acad. Sci. USA *53*, 1238 (1965); *K. G. Brandt* and *G. P. Hess*, Biochem. Biophys. Res. Commun. *22*, 447 (1966).

[69] *G. Feinstein* and *R. E. Feeney*, Biochemistry *6*, 749 (1967).

[70] *T. Chase, Jr.* and *E. Shaw*, Biochem. Biophys. Res. Commun. *29*, 508 (1967).

[71] *N. M. Green*, Biochem. J. *66*, 407 (1957).

[72] *R. J. Peanasky* and *G. M. Abu-Erreish* in [24], p. 281.

[73] *H. Fritz, M. Gebhardt, R. Meister*, and *E. Fink* in [24], p. 271.

[74] *Y. Birk* and *A. Gertler* in [24], p. 142.

[75] *L. Gorini* and *L. Audrain*, Biochim. Biophys. Acta *8*, 702 (1952).

[76] *M. Laskowski, Sr.* and *F. C. Wu*, J. Biol. Chem. *204*, 797 (1953).

[77] *M. Laskowski, Sr., S. L. Schneider, K. A. Wilson, L. F. Kress, J. H. Mozejko, S. R. Martin, U. Kucich* and *M. Andrews* in [24], p. 66.

[78] *H. Tschesche, H. Klein*, and *G. Reidel* in [24], p. 299.

[79] *P. C. Harpel*, J. Exp. Med. *132*, 329 (1970); *J. Gigli, J. W. Mason, R. W. Colman*, and *K. F. Austen*, J. Immunol. *104*, 574 (1970).

[80] *H. Fritz, B. Brey, A. Schmal*, and *E. Werle*, Hoppe-Seylers Z. Physiol. Chem. *350*, 1551 (1969); *H. Fritz, G. Wunderer, K. Kummer, N. Heimburger*, and *E. Werle, ibid.* *353*, 906 (1972).

[81] *J. Lebowitz* and *M. Laskowski, Jr.*, Biochemistry *1*, 1044 (1962); *3*, 469 (1964).

[82] *H. Fritz, I. Trautschold*, and *E. Werle*, Hoppe-Seylers Z. Physiol. Chem. *342*, 253 (1965); *L. W. Nichol* and *D. J. Winzor*, Biochem. Biophys. Acta *94*, 591 (1965); *G. A. Gilbert*, Nature *210*, 299 (1966).

[83] *E. Sheppard* and *A. D. McLaren*, J. Amer. Chem. Soc. *75*, 2587 (1953).

[84] *R. F. Steiner*, Arch. Biochem. Biophys. *49*, 71 (1954).

[85] *D. Millar, K. Minzghor*, and *R. F. Steiner*, Arch. Biochem. Biophys. *65*, 135 (.962).

[86] *I. Schechter* and *A. Berger*, Biochem. Biophys. Res. Commun. *27*, 157 (1967).

[87] *D. Kowalski* and *M. Laskowski, Jr.*, Biochemistry *11*, 3451 (1972).

[88] *K. Ozawa* and *M. Laskowski, Jr.*, J. Biol. Chem. *241*, 3955 (1966).

[89] *R. Haynes* and *R. E. Feeney*, Biochemistry 7, 2879 (1968).

[90] *J. Chauvet* and *R. Acher*, J. Biol. Chem. *242*, 427 (1967).

[91] *L. J. Greene* and *J. S. Giordano, Jr.*, J. Biol. Chem. *244*, 285 (1969); *L. J. Greene* and *D. C. Bartelt, ibid. 244*, 2646 (1969).

[92] *H. Tschesche, E. Wachter, S. Kupfer, R. Obermeier, G. Reidel, G. Haenisch*, and *M. Schneider* in [24], p. 207.

[93] *R. W. Sealock* and *M. Laskowski, Jr.*, Biochemistry *8*, 3703 (1969).

[94] *H. Tschesche* and *Th. Dietl* in [209].

[95] *M. Righi* in [24], p. 74.

[96] *U. DeV. Bidlingmeyer, T. R. Leary*, and *M. Laskowski, Jr.*, Biochemistry *11*, 3303 (1972).

[97] *J. A. Luthy, M. Praissman, W. R. Finkenstadt*, and *M. Laskowski, Jr.*, J. Biol. Chem. *248*, 1760 (1973).

[98] *W. R. Finkenstadt* and *M. Laskowski, Jr.*, J. Biol. Chem. *242*, 771 (1967); *H. F. Hixson, Jr.* and *M. Laskowski, Jr., ibid. 245*, 2027 (1970).

[99] *C. W. Niekamp, H. F. Hixson, Jr.*, and *M. Laskowski, Jr.*, Biochemistry *8*, 16 (1969).

[100] *M. Rigbi* and *L. J. Greene*, J. Biol. Chem. *243*, 5457 (1968).

[101] *H. Tschesche* and *R. Obermeier* in [24], p. 135.

[102] *L. F. Kress, K. A. Wilson*, and *M. Laskowski, Sr.*, J. Biol. Chem. *243*, 1758 (1968).

[103] *M. Laskowski, Jr., R. W. Duran, W. R. Finkenstadt, S. Herbert, H. F. Hixson, Jr., D. Kowalski, J. A. Luthy, J. A. Mattis, R. E. McKee*, and *C. W. Niekamp* in [24], p. 117.

[104] *W. R. Finkenstadt* and *M. Laskowski, Jr.*, Abstracts of Papers, 162nd National Meeting of the Amer. Chem. Soc., Washington D. C., Sept. 1971, No. Biol. 231.

[105] *N. C. Robinson, R. W. Tye, H. Neurath*, and *D. A. Walsh*, Biochemistry *10*, 2743 (1971).

[106] *V. Frattali* and *R. F. Steiner*, Biochem. Biophys. Res. Commun. *34*, 480 (1969).

[107] *F. A. Anderer* and *S. Hörnle*, Ann. N. Y. Acad. Sci. *146*, 381 (1968).

[108] *H. Tschesche* and *G. Reidel*, Diplomarbeit, Technische Universität München 1970.

[109] *D. Shotton*, New Scientist *45*, 546 (1970); in [24], p. 47.

[110] *B. Kassell* and *R. B. Show*, Biochemistry 5, 3449 (1966).

[111] *H. Fritz, E. Fink, M. Gebhardt, K. Hochstrasser*, and *E. Werle*, Hoppe-Seylers Z. Physiol. Chem. *350*, 933 (1969).

[112] *D. Kowalski* and *M. Laskowski, Jr.*, Biochemistry *11*, 3451 (1972).

[113] *H. Fritz, H. Schult, R. Meister*, and *E. Werle*, Hoppe-Seylers Z. Physiol. Chem. *350*, 1531 (1969).

[114] *H. Tschesche, H. Jering*, and *R. Schorp*, unpublished results.

[115] *H. Tschesche* and *E. Wachter*, Hoppe-Seylers Z. Physiol. Chem. *351*, 1449 (1970).

[116] *B. Kassell* and *M. Laskowski, Sr.*, Biochem. Biophys. Res. Commun. *17*, 792 (1964); *B. Kassell, M. Radicevic, M. J. Ansfield*, and *M. Laskowski, Sr., ibid. 18*, 255 (1965); *B. Kassell* and *M. Laskowski, Sr., ibid. 20*, 463 (1965).

[117] *J. Chauvet, G. Nouvel*, and *R. Acher*, Biochim. Biophys. Acta *92*, 200 (1964); *J. Chauvet* and *R. Acher*, Bull. Soc. Chim. Biol. *49*, 985 (1967).

[118] *V. Dlouhá, P. Pospíšilová, B. Meloun*, and *F. Šorm*, Collect. Czech. Chem. Commun. *33*, 1363 (1968).

[119] *F. A. Anderer*, Z. Naturforsch. *20b*, 499 (1965); *F. A. Anderer* and *S. Hörnle*, J. Biol. Chem. *241*, 1568 (1966).

[120] *H. Tschesche* and *E. Wachter*, Eur. J. Biochem. *16*, 187 (1970).

[121] *D. C. Bartelt* and *L. J. Greene*, J. Biol. Chem. *246*, 2218 (1971).

[122] *K. Hochstrasser, W. Schramm, H. Fritz, S. Schwarz*, and *E. Werle*, Hoppe-Seylers Z. Physiol. Chem. *350*, 893 (1969).

[123] *H. Tschesche* and *G. Haenisch*, FEBS Lett. *11*, 209 (1970).

[124] *P. Portmann* and *W. Fraefel*, Helv. Chim. Acta *50*, 2078 (1967).

[125] *W. Fraefel* and *R. Acher*, Biochim. Biophys. Acta *154*, 615 (1968).

[126] *T. Koide, S. Tsunasawa*, and *T. Ikenaka*, J. Biochem. *71*, 165 (1972).

[127] *D. E. Bowman*, Proc. Soc. Exp. Biol. Med. *63*, 547 (1946).

[128] *S. Odani, T. Koide* and *T. Ikenaka*, Proc. Jap. Acad. *47*, 621 (1971).

[129] *G. Jones, S. Moore* and *W. H. Stein*, Biochemistry *2*, 66 (1963); *R. Haynes* and *R. E. Feeney*, J. Biol. Chem. *242*, 5378 (1967).

[130] *C. G. L. Tan* and *F. C. Stevens*, Eur. J. Biochem. *18*, 503, 515 (1971).

[131] *K. Hochstrasser, K. Illchmann*, and *E. Werle*, Hoppe-Seylers Z. Physiol. Chem. *351*, 1503 (1970).

[132] *K. Hochstrasser, K. Illchmann*, and *E. Werle*, Hoppe-Seylers Z. Physiol. Chem. *351*, 721 (1970).

[133] *M. O. Dayhoff* and *R. V. Eck*: Atlas of Protein Sequence and Structure. National Biomedical Research Foundation, Silver Spring, Maryland 1972, D-169.

[134] *L. J. Greene* and *O. Guy* in [24], p. 201.

[135] *O. Guy, R. Shapanka*, and *L. J. Greene*, J. Biol. Chem. *2446*, 7740 (1971).

[136] *H. Tschesche, M. Schneider, G. Reidel*, and *H. Klein*, Hoppe-Seylers Z. Physiol. Chem. *353*, 763 (1972).

[137] *A. Induni*, Dissertation, Université de Fribourg (Switzerland) (1969); *A. Induni* in [24], p. 879.

[138] *J. R. Brown, N. Lerman*, and *Z. Bohak*, Biochem. Biophys. Res. Commun. *23*, 561 (1966).

[139] *R. Huber, D. Kukla, A. Rühlmann, O. Epp*, and *H. Formanek*, Naturwissenschaften *57*, 389 (1970).

[140] *R. Huber, D. Kukla, A. Rühlmann*, and *W. Steigemann* in [24], p. 56.

[141] *R. Huberr, D. Kukla, A. Rühlmann*, and *W. Steigemann*, Cold Spring Harbor Symp. Quant. Biol. *36*, 141 (1971).

[142] *D. M. Blow, C. S. Wright, D. Kukla, A. Rühlmann, W. Steigemann*, and *R. Huber*, J. Mol. Biol. *69*, 137 (1972).

[143] *R. M. Stroud, L. M. Kay*, and *R. E. Dickerson*, Cold Spring Harbor Symp. Quant. Biol. *36*, 125 (1971).

[144] *R. Henderson*, J. Mol. Biol. *54*, 341 (1970).

[145] *D. M. Blow, J. J. Birktoft*, and *B. S. Hartley*, Nature *221*, 337 (1969).

[146] *R. E. Feeney* in [24], p. 162.

[147] *G. Feinstein* and *R. E. Feeney*, J. Biol. Chem. *241*, 5183 (1966).

[148] *R. J. Foster* and *C. A. Ryan*, Fed. Proc. *24*, 473 (1965).

[149] *V. Dlouha* and *B. Keil*, FEBS Lett. *3*, 137 (1969).

[150] *J. P. Vincent* and *M. Lazdunski*, Biochemistry *11*, 2967 (1972).

[151] *H. Fritz, H. Schießler, B. Jörg-Brey, H. Tschesche*, and *E. Fink*, Hoppe-Seylers Z. Physiol. Chem. *353*, 1013 (1972).

[152] *H. Fritz, B. Förg-Brey, M. Meier, M. Arnhold*, and *H. Tschesche*, Hoppe-Seylers Z. Physiol. Chem. *353*, 1950 (1972).

[153] *C. C. Yip*, Proc. Nat. Acad. Sci. USA *68*, 1312 (1971).

[154] *H. Tschesche* and *F. Fiedler*, unpublished results.

[155] *R. E. Feeney, G. E. Means*, and *J. C. Bigler*, J. Biol. Chem. *244*, 1957 (1969).

[156] *C. Figarella, G. A. Negri*, and *O. Guy*, personal communication.

[157] *L. J. Greene* and *M. H. Pubols* in [24], p. 196.

[158] *F. C. Wu* and *M. Laskowski, Sr.*, J. Biol. Chem. *213*, 609 (1955).

[159] *H. Deisenhoferr* and *W. Steigemann*, unpublished results.

[160] *N. Sevilla* and *M. Rigbi*, Israel J. Chem. 7, 130p (1969).

[161] *T. Ogawa, T. Higasa*, and *T. Hata*, Agr. Biol. Chem. *32*, 484 (1968).

[162] *Y. Birk, A. Gertler*, and *S. Khalef*, Biochim. Biophys. Acta *147*, 402 (1967).

[163] *C. A. Ryan* and *J. J. Clary*, Arch. Biochem. Biophys. *108*, 169 (1964).

[164] *F. C. Stevens*, Proc. Can. Fed. Biol. Soc. *12*, 16 (1969).

[165] *R. Haynes* and *R. E. Feeney*, J. Biol. Chem. *242*, 5378 (1967); *R. Haynes, D. T. Osuga*, and *R. E. Feeney*, Biochemistry 6, 541 (1967).

[166] *A. Puztai*, Eur. J. Biochem. 5, 252 (1968).

[167] *Y. Tomimatsu, J. J. Clary*, and *J. J. Burtulovich*, Arch. Biochem. Biophys. *115*, 536 (1966).

[168] *M. B. Rhodes, N. Bennett*, and *R. E. Feeney*, J. Biol. Chem. *235*, 1686 (1960).

[169] *T. W. Mehl, W. O'Connell*, and *J. Degroot*, Science *145*, 821 (1964).

[170] *B. J. Haverback, B. Dyce, H. F. Bundy, S. K. Wirtschafter*, and *H. A. Edmondson*, J. Clin. Invest. *41*, 972 (1962).

[171] *P. J. Burck, R. L. Hamill, E. W. Cerwinsky*, and *E. L. Grinnan*, Biochemistry 6, 3180 (1967).

[172] *H. Tschesche, S. Kupfer, O. Lengel, M. Meier, H. Fritz*, and *R. Klauser* in [209].

[173] *B. Kassell* and *M. Laskowski, Sr.*, Fed. Proc. *24*, 593 (1965).

[174] *B. Kassell* and *T.-W. Wang* in [24], p. 89.

[175] *H. Tschesche, M. Schneider*, and *G. Reidel* in [209].

[176] *Y. Shain* and *A. M. Mayer*, Physiol. Plant. *18*, 853 (1965).

[177] *V. Mansfeld, A. Ziegelhöffer, Z. Horakova*, and *J. Hladevec*, Naturwissenschaften *46*, 172 (1959).

[178] *E. Werle*, Hoppe-Seylers Z. Physiol. Chem. *338*, 228 (1964).

[179] *M. Laskowski, Jr.* and *M. Laskowski, Sr.*, J. Biol. Chem. *190*, 563 (1951); *M. Laskowski, Sr., B. Kassell*, and *G. Hagerty*, Biochim. Biophys. Acta *24*, 300 (1957).

[180] *L. Schneider* and *J. Szathmary*, Z. Immunitätsforsch. *94*, 465 (1938); *95*, 169, 177, 189 (1939); *98*, 24 (1940).

[181] *H. Fritz, B. Förg-Brey, E. Fink, H. Schiessler, E. Jaumann*, and *M. Arnhold*, Hoppe-Seylers Z. Physiol. Chem. *353*, 1007 (1972); *H. Fritz, B. Förg-Brey, M. Meier, M. Arnhold*, and *H. Tschesche, ibid. 353*, 1950 (1972).

[182] *L. J. D. Zaneveld, R. T. Robertson, M. Kessler*, and *W. L. Williams*, J. Reprod. Fert. *25*, 387 (1971).

[183] *R. L. Stambaugh* in *K. S. Moghissi* and *E. S. E. Hafez:* Biology of Mammalian Fertilization and Implantation. Charles C. Thomas, Springfield, Ill. 1972.

[184] *H. Fritz, E. Fink*, and *R. Marx* in *R. Marx* and *H. A. Thies:* Sexualhormone und Blutgerinnung. Schattauer, Stuttgart 1971, p. 33.

[185] *L. J. Zanefeld, R. T. Robertson*, and *W. L. Williams*, FEBS Lett. *11*, 345 (1970).

[186] *R. Stambaugh, B. G. Bracket*, and *L. Mastroiani*, Biol. Reprod. *1*, 223 (1969).

[187] *H. Haendle, H. Fritz, I. Trautschold*, and *E. Werle*, Hoppe-Seylers Z. Physiol. Chem. *343*, 185 (1965).

[188] *J. Bodman*, Clin. Chim. Acta *3*, 108 (1958).

[189] *E. Geiringer*, Proc. Soc. Exp. Biol. Med. *108*, 658 (1961); *P. G. Stansley* and *D. S. Ramsey*, Cancer Res. *17*, 572 (1957); *J. S. Ram, L. Terminiello, M. Bier*, and *F. F. Nord*, Arch. Biochem. Biophys. *52*, 451 (1954).

[190] *G. F. B. Schumacher* in [24], p. 253.

[191] *F. Fritz, N. Heimburger, M. Meier, M. Arnhold, L. J. D. Zaneveld*, and *G. F. B. Schumacher*, Hoppe-Seylers Z. Physiol. Chem. *353*, 1953 (1972).

[192] *J. M. Bedford*, Reprod. Biology. Excerpta Medica, Amsterdam 1972; *K. Conrad, J. Buckley*, and *R. J. Stambaugh*, J. Reprod. Fert. *27*, 133 (1971).

[193] *H. Tschesche, A. v. Rücker, H. Schiessler*, and *H. Fritz*, unpublished results.

[194] *C. B. Laurell* and *S. Eriksson*, Clin. Chim. Acta *11*, 395 (1965); *S. Eriksson*, Acta Med. Scand. *177*, Suppl. 432 (1965).

[195] *C. A. Ryan*, Biochem. Biophys. Res. Commun. *44*, 1265 (1971).

[196] *K. Hochstrasser, H. Feuth*, and *E. Werle*, Hoppe-Seylers Z. Physiol. Chem. *353*, 855 (1972).

[197] *B. M. Braganza, Y. M. Sambray*, and *R. J. Sambray*, Eur. J. Biochem. *13*, 410 (1970).

[198] *A. Rühlmann, D. Kukla, P. Schwager, K. Bartels*, and *R. Huber*, J. Mol. Biol *77*, 417 (1973).

[199] *J. J. Birktoft* and *D. M. Blow*, J. Mol. Biol. *68*, 187 (1972).

[200] *R. M. Sweet, J. Janin*, and *D. M. Blow* in [209].

[201] *R. Henderson, C. S. Wright, G. P. Hess*, and *D. M. Blow*, Cold Spring Harbor Symp. Quant. Biol. *36*, 63 (1971).

[202] *H. Fritz, E. Haumann, R. Meister, P. Pasquay, K. Hochstrasser*, and *E. Fink* in [24], p. 257.

[203] *H. Tschesche, O. Lengel, W. D. Schleuning*, and *H. Fritz*, unpublished results.

[204] *L. F. Kress* and *M. Laskowski, Sr.* in [209]; *N. Heimburger*, personal communication.

[205] *S. L. Schneider* and *M. Laskowski, Sr.*, in [209].

[206] *H. Haendle, H. Ingrisch*, and *E. Werle*, Hoppe-Seylers Z. Physiol. Chem. *351*, 545 (1970).

[207] *N. Heimburger* and *H. Trobisch*, Angew. Chem. *83*, 89 (1971); Angew. Chem. internat. Edit. *10*, 85 (1971).

[208] *H. D. Belitz, H. P. Wassner*, and *J. Weder*, Z. Lebensm.-Unters. Forsch. *137*, 211 (1968); *H. H. Ortanderl* and *H. D. Belitz*, Lebensm.-Wiss. Technol. *4*, 85 (1971); *J. Weder* and *H. D. Hory, ibid. 5*, 54, 86 (1972).

[209] *H. Fritz, H. Tschesche, L. J. Greene*, and *E. Truscheit:* Proteinase Inhibitors. Proceedings of the Second International Research Conference – Bayer Symposium V. Springer, Berlin 1974, in press.

[210] *K. A. Wilson* and *M. Laskowski, Sr.* in [209].

[211] *T. R. Leary* and *M. Laskowski, Jr.*, Abstract Papers, Amer. Chem. Soc. Meeting 1973.

[212] *D. Kowalski, T. R. Leary, R. E. McKee, R. W. Sealock, D. Wang*, and *M. Laskowski, Jr.* in [209].

[213] *H. Tschesche* and *H. Jering* in [209].

[214] *H. Tschesche* and *T. Dietl* in [209].

[215] *T. Dietl* and *H. Tschesche*, Eur. J. Biochem., in press.

[216] *T. R. Green* and *C. A. Ryan*, Science *175*, 776 (1972).

[217] *C. A. Ryan* in [209].

[218] *H. P. Schnebli* and *M. Burger* in [209].

[219] *H. Tschesche, K. Kolb, E. Standl*, and *T. Dietl* in [209].

[220] *J. S. Brush* and *H. Tschesche* in [209].

[221] *J. S. Brush*, Biochem. Biophys. Res. Commun. *53*, 894 (1973).

[222] *R. Shainkin* and *Y. Birk*, Biochim. Biophys. Acta *221*, 502 (1970).

[223] *A. A. M. Gribnau, J. G. G. Shoenmaker, M. van Kraaikamp, M. Hilak*, and *H. Bloemendal*, Biochim. Biophys. Acta *224*, 55 (1970); *A. A. Gribnau, J. G. G. Shoenmakers, M. van Kraaikamp*, and *H. Bloemendal*, Biochem. Biophys. Res. Commun. *38*, 1068 (1970); *P. Lesca* and *C. Paoletti*, Proc. Nat. Acad. Sci. USA *64*, 913 (1969); *U. S. Shapot, I. A. Chudinova, G. D. Krechetova*, and *I. Pushina*, FEBS Lett. *13*, 13 (1971).

[224] *T. Ikenaka, S. Odani, M. Sakai*, and *Y. Nabeshima* in [209].

[225] *P. Hao Yu, M. R. Kula*, and *H. Tsai*, Eur. J. Biochem. submitted for publication.

[226] *R. C. Roberts, W. A. Riesen*, and *P. K. Hall* in [209].

[227] *J. A. Mattis* and *M. Laskowski, Jr.*, Biochemistry *12*, 2239 (1973).

[228] *S. Odani, T. Koide*, and *T. Ikenaka*, J. Biochem. *71*, 831 (1972).

[229] *S. Odani* and *T. Ikenaka*, J. Biochem. *71*, 839 (1972).

[230] *S. Odani* and *T. Ikenaka*, J. Biochem. *74*, 697 (1973).

[231] *H. Jering* and *H. Tschesche*, unpublished results.

[232] *R. W. Sealock* and *M. Laskowski, Jr.*, Biochemistry *12*, 3139 (1973).

[233] *J. Krah* and *F. C. Stevens*, Biochemistry *11*, 1804 (1972); *12*, 1330 (1973).

[234] *F. C. Stevens, S. Wuerz*, and *J. Krah* in [209].

[235] *D. J. Strydom*, Nature New Biology *243*, 88 (1973).

[236] *H. Takahashi, S. Iwanaga, Y. Hokama, T. Suzuki*, and *T. Kitawaga* in [209].

[237] *M. Laskowski, Jr., private communication, and M. Laskowski, Jr. et al.* in [209].

[238] *L. J. Greene* and *D. C. Bartelt* in [209].

[239] *S. Odani* and *T. Ikenaka*, J. Biochem. *74*, 857 (1973).

[240] *T. Koide* and *T. Ikenaka*, Eur. J. Biochem. *32*, 401 (1973); *ibid. 32*, 417 (1973).

[241] *T. Koide, S. Tsunazawa*, and *T. Ikenaka*, Eur. J. Biochem. *32*, 408 (1973).

[242] *R. Huber, D. Kukla, W. Steigemann, J. Deisenhofer*, and *A. Jones* in ref. [209].

[243] *R. J. Peanasky, G. M. Abu-Erreish, C. R. Gaush, G. A. Homandberg, D. O'Heeron, R. K. Linkenheil*, and *U. Kucich* in [209].

[244] *H. Schweitz, J. P. Vincent*, and *M. Lazdunski*, Biochemistry *12*, 2841 (1973).

[245] *J. P. Vincent* and *M. Lazdunski*, Eur. J. Biochem. *38*, 365 (1973).

[246] *M. Laskowski, Jr. et al.* in [209].

[247] *M. Lazdunski, J. P. Vincent, H. Schweiz, M. Peron-Renner*, and *J. Pudles* in [209].

[248] *J. Engel, U. Quast, H. Heumann, G. Krause*, and *E. Steffen* in [209].

[249] *E. Werle* in [24].

Activation of Molecular Oxygen[**]

By G. Henrici-Olivé and S. Olivé[*]

Molecular oxygen as a ligand in transition metal complexes is of interest for biochemistry, and for inorganic and organometallic chemistry. Several examples of O_2 complexes, as well as the kinetics and mechanism of their formation are presented. The influence of other ligands on the activation of O_2 is discussed on the basis of a MO description of the electronic structure of the oxygen molecule and of the bonding within the metal-oxygen complexes. Reactions of coordinated oxygen are described.

1. Introduction

The fixation and activation of molecular oxygen on soluble transition metal compounds is a topic of current interest. In fact, the oxygen molecule itself is a relatively reactive entity. It forms compounds with nearly all elements, one of the consequences being that the earth's crust contains about 50% by weight of bound oxygen. What do we really mean then by "activation of molecular oxygen"?

One challenge comes from biochemistry. The respiratory pigments are able to fix oxygen molecules from the atmosphere, to transport them to their sites of reaction, and there to release them. This, in a sense, is a catalytic process, since the natural "oxygen carriers" (*e.g.* hemoglobins, hemocyanines) are not irreversibly oxidized during the process, but retain their activity. Although it appears well established that transition metals (particularly iron) play an important role, our knowledge about the structure of the natural metal complexes involved, the bonding of the oxygen, and the valency state of the metal is still poor. Investigation of the natural products is complicated by their macromolecular protein component. Therefore, low-molecular model substances containing a transition metal center and being able to combine reversibly with oxygen have attracted considerable interest.

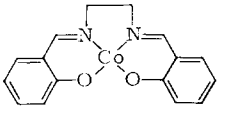
Presumably not only the reversibility but also in particular the activation of the oxygen molecule are of importance in natural systems. Obviously, the oxygen has to react with substrate molecules once it has been transported by the hemoglobin to the site of its action. Thus the question arises: is the O_2 molecule also activated in the synthetic oxygen complexes and, if so, can the chemist make use of this activated oxygen for scientifically or technically interesting oxidation reactions? Present commercial processes for the oxidation of olefins are generally based on heterogeneous catalysis. Selectivity appears to be especially critical[1]. Thus, it would certainly be a rewarding goal to use oxygen fixed at soluble transition metal species for catalytic and specific oxidation of substrates such as olefins or amines, which could be introduced into the metal-oxygen complex as ligands. Several approaches of this kind have already been undertaken.

2. Oxygen-Metal Complexes

A great number of transition metal complexes with oxygen as a ligand are known. As early as 1852 *Fremy*[2] reported that "ammonia-cobalt salts", and particularly the nitrate, absorb oxygen from the air, and release it again when dissolved in water. But it was a long way from there to the more sophisticated cobalt(II) chelates, which are considered today as suitable model substances for the natural oxygen carrier systems, and to the catalytically active transition metal-oxygen complexes. Competent reviews[3-8] describe this way, which can only be high-lighted here.

2.1. Oxygen-Cobalt Complexes

By far the greatest number of synthetic oxygen complexes are based on cobalt, and one of the most thoroughly investigated systems is the chelate complex [2,2'-ethylenebis(nitrilomethylidine)diphenolato]cobalt(II) (Co(salen)) *(1)* and its many derivatives.



(1)

Early investigations concentrated on reversible oxygenation in the solid state[9]. The compound *(1)* is perfectly planar, and crystallizes in a layer lattice[*]. The oxygen uptake occurs in the ratio $Co:O_2=2:1$, and it is assumed that the O_2 molecule is bound between two layers by two cobalt atoms, one in each layer. The oxygen can be removed from the complex by mere heating. The reversibility is astonishing: up to 3000 oxygenation-deoxygenation cycles have been carried out with the same sample; after 300 cycles the remaining activity was 70%[10], after 3000 cycles 50%[11]. There have even been efforts to develop the Co(salen) system to a technical process for the production of oxygen from air[4,10], but so far it does not appear that this would be able to compete with the Linde process.

In the meantime it has been found that Co(salen) and its ring-substituted derivatives form reversible oxygen adducts also in solution, in certain aprotic complexing solvents such as dimethylformamide (DMF) or dimethyl sulfoxide (DMSO), or in non-complexing solvents in the presence of strong bases such as pyridine or DMF. Depending on the chelating ligand, on the solvent, or on the added base, and on the temperature, the formation of binuclear complexes ($Co:O_2=2$) or mononuclear complexes ($Co:O_2=1$) has been observed[12-14]. Mostly the ratio $Co:O_2$ has been judged from the

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[**] Sections of this progress report have been taken from the following book due for publication in 1974 by Verlag Chemie, Weinheim: *G. Henrici-Olivé* and *S. Olivé*: Homogeneous Catalysis with Transition Metal Complexes.

[*] There are other crystalline modifications of the compound which are less, or not at all, active for O_2 uptake.

oxygen uptake. However, some of the adducts have also been isolated in pure form, and it was found that one solvent (or base) molecule is incorporated per Co center. Hence, the related oxygenation equilibria can be formulated as, *e.g.*:

$$\text{Co(3-methoxy-salen)} + L + O_2 \rightleftharpoons \text{Co(3-methoxy-salen)}LO_2$$

(adduct isolated with L = pyridine), and

$$2\,\text{Co(salen)} + 2L + O_2 \rightleftharpoons (\text{Co(salen)})_2L_2O_2$$

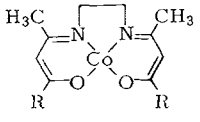
(adduct isolated with L = DMF or DMSO)[12].

X-ray structural analysis of the binuclear adduct with DMF has shown that the oxygen molecule forms a bridge between the two cobalt centers:

DMF(salen)Co—O—O—Co(salen)DMF

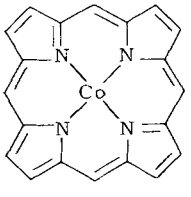
The coordinating ligands about the cobalt atoms form distorted octahedra. The equatorial positions are occupied by the quadridentate salen ligand. The DMF molecule is bonded in an axial position through its oxygen atom, the other axial position being occupied by one of the oxygen atoms of the O_2 bridge[15].

A similar chelate, [4,4'-ethylenedinitrilodi-2-pentanonato]cobalt(II) (Co(acacen)) *(2a)*, also forms reversible 1:1 adducts in non-aqueous solvents and in the presence of a base such as pyridine or dimethylformamide, although only at $T<0$ °C[16].

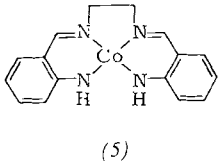


(2a), R = CH_3
(2b), R = C_6H_5

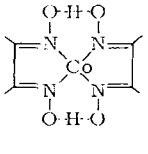
In the natural oxygen carriers the metal is surrounded by four nitrogen ligands, iron in hemoglobin for instance by the characteristic system of four pyrrole rings (porphyrin). Co-porphyrins *(3)* in fact also fix molecular oxygen reversibly[17], and bis(2,3-butanedionedioximato)cobalt(II) *(4)* ("cobaloxime") does the same[18]. However, the chelate complex [2,2'-ethylenebis(nitrilomethylidine)dianilido]cobalt(II) (Co(amben)) *(5)*, although structurally similar to Co(salen), fails to react with oxygen[17], and phthalocyanine-Co *(6)*, although similar to the porphyrins in the immediate vicinity of the metal, does not react either[17,19]. These few examples indicate that the electronic requirements for the fixation of oxygen appear to be rather critical.



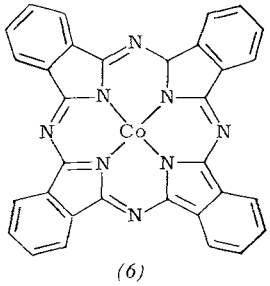
(3)



(5)

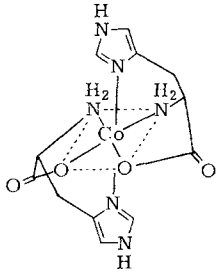


(4)



(6)

Bis(histidinato)cobalt(II) *(7)* is different from the cobalt species mentioned so far, since no free coordination site is available. Nevertheless a binuclear complex with O_2 is formed in water. Presumably the O_2 molecule displaces the carboxylate group of one of the histidine ligands[20,21]. A variety of cobalt(II) complexes with other amino acids and with dipeptides have also been shown to take up oxygen reversibly[3,4].

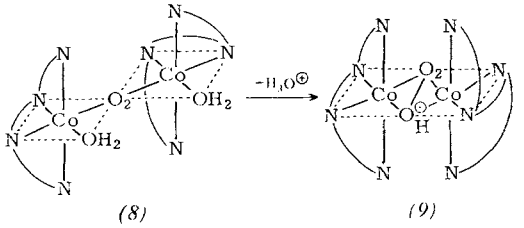


(7)

A further important class of cobalt complexes able to fix molecular oxygen is found in the hexaminecobalt(II) ion and related compounds. The ion $[Co(NH_3)_6]^{2+}$, which historically was the first example to be investigated[2,22], is oxygenated in aqueous ammonia, the oxygen displacing one of the NH_3 ligands. A brown binuclear complex, with bridging O_2, is formed; decrease of the oxygen pressure or increase of the ammonia concentration deoxygenates the complex[4]:

$$2[Co(NH_3)_6]^{2+} + O_2 \rightleftharpoons [(NH_3)_5CoO_2Co(NH_3)_5]^{4+} + 2NH_3$$

Chelating aliphatic amines such as ethylenediamine (en), diethylenetriamine (dien), or triethylenetetramine (trien) can replace the ammonia as ligand[23], but the oxygenated complexes then have a certain tendency to undergo subsequent processes which are accompanied by color changes and can be followed spectrophotometrically[24]. In the case of the quadridentate ligand trien, the rapid reversible formation of complex *(8)* is followed by a slow irreversible transformation to what is assumed to be the dibridged species *(9)* with an additional bridging OH group[24,25]. Complex *(9)* is very stable; only on acidification does it decompose to Co^{II}trien, O_2, and H_2O. Evidence for dibridged complexes has also been reported with other nitrogen ligands[26,27].



(8) *(9)*

In other cases, subsequent irreversible oxidation of Co^{II} to Co^{III} with formation of hydrogen peroxide is found, particularly with dien as ligand[26,28]:

$$\text{dien}Co^{II}O_2Co^{II}\text{dien} \xrightarrow{H^+} 2\,\text{dien}Co^{III} + H_2O_2$$

2.2. Oxygen Complexes of Other Transition Metals

The number of oxygen complexes with other transition metals is relatively small as compared with those of cobalt[7, 8].

After *Vaska*'s discovery[29] that the complex $Ir(CO)(Cl)(P(C_6H_5)_3)_2$ in benzene solution reversibly takes up molecular oxygen, forming a 1:1 adduct, several similar complexes have been reported by a number of authors[8]. So far, they are restricted to Group VIII metals, particularly Ru, Os, Rh, and Ir. All have triphenylphosphane or related ligands ($C_6H_5PR_2$, $As(C_6H_3)_3$, $Sb(C_6H_5)_3$, *etc.*). The chlorine ligand may be replaced by Br, I, OH, NO_3, N_3, CN, NCO, or NCS; instead of CO, the complexes may contain NO, or this neutral ligand may be missing. Other related complexes, giving also reversible 1:1 adducts, are $[Rh\{(C_6H_5)_2PCH_2CH_2P(C_6H_5)_2\}_2][PF_6]$[30], and $Ru(Cl_2)(As(C_6H_5)_3)_3$[31].

Several other transition metal complexes have been found to form irreversible, relatively stable oxygen complexes, *e.g.* the iridium analog of the rhodium complex mentioned above[30], and also $M(P(C_6H_5)_3)_2$ with M = Ni(0), Pt(0), or Pd(0) gives irreversible mononuclear oxygen complexes[32]. Another stable rhodium complex was reported to be binuclear, having a bridging O_2 molecule:

$Cl(py)_2Rh{-}O{-}O{-}Rh(py)_2Cl$ (py = pyridine) [33]

One may safely predict that the catalog of oxygen fixing transition metal species (particularly of Group VIII metals) will greatly increase in the future. Today the discovery of such complexes appears to be still more or less accidental, but with increasing knowledge of ligand influences on bonding properties it will probably become possible to estimate which environment could make a certain metal ion susceptible to oxygen uptake.

2.3. Kinetics and Mechanism of Oxygen Uptake

It appears now generally agreed that the binuclear, O_2-bridged complexes are formed in a two step mechanism[12, 13, 21]:

$$Co^{II} + O_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Co^{II}O_2 \quad (1)$$

$$Co^{II}O_2 + Co^{II} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} Co^{II}O_2Co^{II} \quad (2)$$

(Ligands are omitted for the sake of simplicity of formulas)

Wilkins et al. accumulated kinetic evidence for the above mechanism from studies on cobalt(II) complexes with various nitrogen-containing ligands in water[21, 25, 26]. Although in these cases the formation of the mononuclear intermediate has not been observed directly, the rate of oxygen uptake is best accommodated by formation of such an intermediate according to eq. (1). The binuclear bridged species have strong absorption peaks in the region 350—420 nm. Their formation was studied by mixing oxygen-free solutions of the cobalt(II) chelates with oxygen-saturated water in a stopped-flow apparatus, and following the increase in optical density in the region mentioned. A large excess of the Co species compared with the oxygen concentration ensured pseudo-first order conditions and complete consumption of the molecular oxygen (*i.e.* reverse reactions are maintained negligible). Formation of the bridged complex obeyed first order kinetics over several half lives (empirical rate constant k_{obs}). Assuming steady state conditions for the intermediate, the following rate law applies for the mechanism given by eqs. (1) and (2):

$$\frac{d[CoO_2Co]}{dt} = \frac{k_1 k_2 [Co]^2 [O_2]}{k_{-1} + k_2 [Co]} = k_{obs}[O_2] \quad (3)$$

This equation indicates that a non-linear dependence of the experimental rate constant k_{obs} on the concentration of the starting cobalt(II) compound is required by the assumed mechanism. Eq. (3) may be rearranged to give:

$$\frac{[Co]}{k_{obs}} = \frac{1}{k_1} + \frac{k_{-1}}{k_1 k_2 [Co]} \quad (4)$$

In fact the plot of $[Co]/k_{obs}$ *versus* $1/[Co]$ was found to be linear, corroborating the two-step mechanism.

In non-aqueous solvents, mononuclear complexes have been observed and even isolated in several cases (see Sections 2.1 and 2.2). The preponderance of the mono- or the binuclear complex appears to be governed by the relative values of the related rate constants, and in certain cases by different solubilities of the two species (*e.g.* poor solubility of the binuclear complex would shift both equilibria, eqs. (1) and (2), to the right).

In the presence of excess oxygen, evidence has been found for a third equilibrium[13]:

$$CoO_2Co + O_2 \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} 2CoO_2 \quad (5)$$

It has been postulated that the 1:1 species resulting from eq. (1) and from eq. (5) would be different in their electronic distribution (formulated $Co^{III}O{-}O^*$ and $Co^{II}O_2$ respectively), and that the stable 1:1 complexes would always arise from eq. (5). Further clarifying work appears necessary (cf. also Section 3).

3. The Bonding of Oxygen to Metal

3.1. The Electronic Structure of the Oxygen Molecule

Figure 1 shows the molecular orbital energy level diagram for a homonuclear diatomic molecule, taking into account the symmetry-allowed interaction between σ_s and σ_p orbitals (see, *e.g.* [34]). The electronic configuration of the oxygen atom is s^2p^4; hence 12 electrons have to be placed into this scheme, leading to the configuration $(2\sigma_g)^2(2\sigma_u)^2(1\pi_u)^4(3\sigma_g)^2(1\pi_g)^2$. Since the $1\pi_g$ level is degenerate, each of the two electrons occupies one of the two orbitals, *i.e.* the free oxygen molecule has two unpaired electrons, and therefore is paramagnetic. The two unpaired electrons confer the character of a biradical upon the molecule in its ground state. Consequently, the predilected reaction partners of O_2 are radicals and paramagnetic metal ions.

The molecular orbital diagram given in Figure 1 is valid for a free oxygen molecule. For O_2 under the influence of the electrostatic field of a transition metal ion in a complex the situation may be somewhat different. It was first postulated by *Griffith*[35] that this influence might remove the degeneracy of the $1\pi_g$ level, and that in certain cases the energy difference

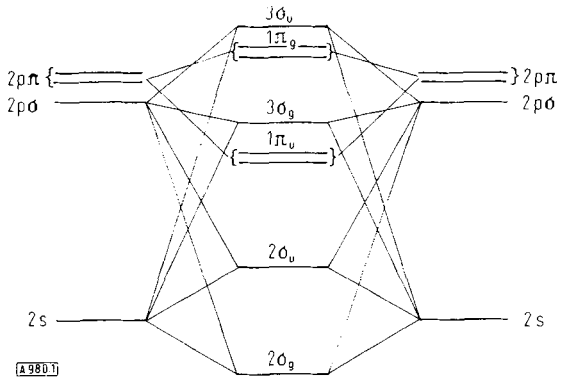


Fig. 1. Molecular orbital energy level diagram for a homonuclear diatomic molecule of the first short period, with σ_s-σ_p interaction.

between the two orbitals may become larger than the energy of pairing, *i.e.* the two electrons will then be located in the more stabilized of the two orbitals with their spins paired (Fig. 2).

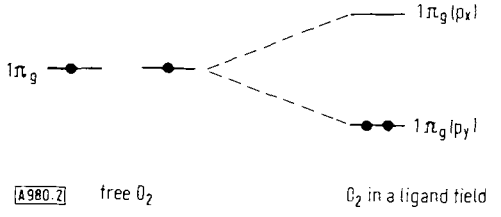


Fig. 2. Influence of a ligand field on the electron distribution in the oxygen molecule.

Griffith has also indicated that in this situation the oxygen molecule has an electronic configuration comparable with that of ethylene in its ground state. We may therefore visualize the electron distribution in terms of a trigonal sp^2 hybridization at the two oxygen atoms. One of the sp^2 hybrid orbitals of each oxygen atom is used for mutual σ bonding and the other two are each doubly occupied; in other words, they form a set of four lone pair orbitals (n_O) oriented in the same way as the four hydrogen atoms in ethylene (see Fig. 3). In molecular orbital language that means that the four lone pair orbitals are linear combinations of $2\sigma_u$, $3\sigma_g$, $1\pi_u(p_y)$ and $1\pi_g(p_y)$, so oriented as to minimize interorbital electronic interaction, whereas $2\sigma_g$ is responsible for the σ bond. There is also one effective π bond in the molecule, $1\pi_u(p_x)$; the lowest energy, empty antibonding orbital is $1\pi_g(p_x)$.

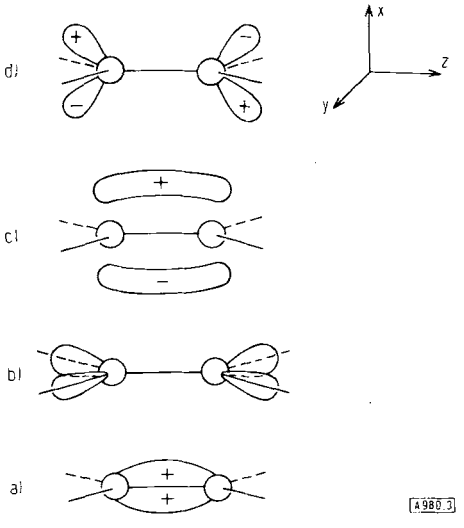


Fig. 3. The "valence state" molecular orbitals of the oxygen molecule: a) σ-bonding MO; b) sp^2 lone pair orbitals (n_O); c) π-bonding MO, $1\pi_u(p_x)$; d) π^*-antibonding MO, $1\pi_g(p_x)$ (according to [35]).

3.2. Structure and Bonding in the Complexes

X-Ray structural analysis, optical spectroscopy, magnetic measurements, and theoretical MO considerations have shed some light onto the bonding in transition metal-oxygen complexes.

We shall first discuss the mononuclear complexes resulting from the interaction of oxygen with Schiff base cobalt(II) compounds, such as Co(salen) *(1)* or Co(acacen) *(2a)*. The non-oxygenated starting materials are paramagnetic, having one unpaired electron per Co center (low spin d^7 configuration)[36]. As mentioned in Section 2.1, a strongly coordinating axial ligand is necessary in order to enable these compounds to become oxygenated in solution. The purpose of the axial ligand may be rationalized considering the d-orbital energy levels of cobalt in different environments (see Fig. 4). In the square planar starting material, d_{xz}, d_{yz}, and d_{z^2} are the most stable orbitals, and the unpaired electron is located in the d_{xy} level, where it is not available for an approaching O_2 molecule. (The x and y axes are in the plane defined by Co and the Schiff base ligand.) A strong axial fifth ligand leads to a square pyramidal arrangement; it raises the d_{z^2} orbital above the d_{xy} level, thus resulting in the electronic configuration $(d_{xz})^2(d_{yz})^2(d_{xy})^2(d_{z^2})^1$[37].

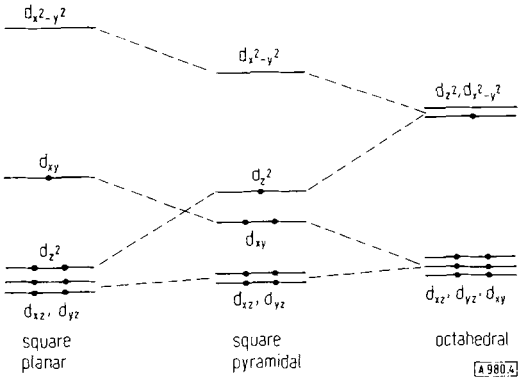


Fig. 4. Energy levels of the d orbitals in various environments.

This latter configuration appears to be a necessary prerequisite of oxygenation[36, 38]. This view is supported by EPR studies. In the presence of a Lewis base, *e.g.* pyridine, Co(acacen) and related compounds have similar EPR signals. Figure 5 shows the spectrum of Co(acacen)py in frozen toluene solution at 77 °K[36]. It indicates the interaction of the unpaired electron with the ^{59}Co nucleus ($I=7/2$) and with the ^{14}N nucleus of the pyridine ligand ($I=1$). The signal is best interpreted assuming that the unpaired electron is associated with the $3d_{z^2}$ orbital[36, 38]. In the absence of such base (no oxygenation!) a different EPR signal is observed which can be fitted to the configuration $(d_{xz})^2(d_{yz})^2(d_{z^2})^2(d_{xy})^1$[38].

After oxygenation the complexes still have one unpaired electron per Co center[16, 36]. Since Co^{II} has one, and gaseous O_2 has two unpaired electrons, spin pairing must have occurred. The best interpretation of this phenomenon would appear to assume that upon coordination the symmetry of the oxygen molecule is sufficiently reduced to split the other-

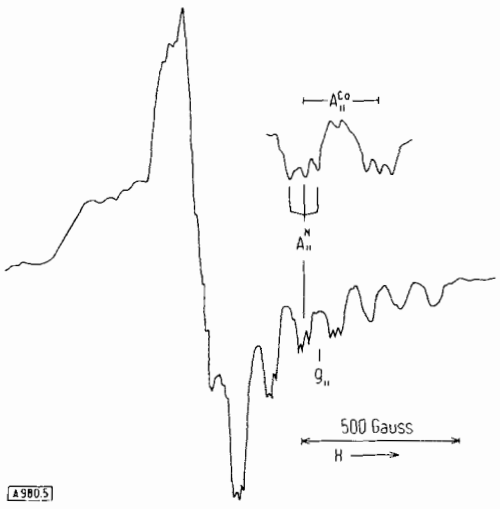


Fig. 5. EPR spectrum of Co(acacen)py in frozen toluene solution at 77 K (after [36]).

wise degenerate antibonding $1\pi_g$ orbitals and to constrain the two antibonding electrons to be paired in the more stable of the two[35, 36] (cf. Fig. 2).

The EPR of the oxygenated complex (Fig. 6) indicates that the unpaired electron has only a small spin density at the Co nucleus ($a_{Co} \approx 10$ gauss as compared with 80—100 gauss for the non-oxygenated parent compounds, Fig. 5). It may be concluded that the unpaired electron is delocalized onto the oxygen ligand, thus making it similar to a superoxide ion. This would mean that the complex approaches the formulation $Co^{III}(O_2^-)$. The very fact, however, that the unpaired electron has a definite spin density at the Co nucleus shows clearly that the assignment of integral oxidation numbers is meaningless in this kind of bonding. The situation appears to be better described by stating that the unpaired electron moves in a molecular orbital made up of a 3d atomic orbital of Co and the empty antibonding π orbital of O_2:

$$\psi = c_1 3d_{Co} + c_2 1\pi_g(p_x) \qquad \text{with } c_2 > c_1 \qquad (6)$$

The X-ray structural analysis of a related mononuclear cobalt-oxygen complex, Co(bzacen)pyO_2 [Co(bzacen)=*(2b)*, py = pyridine] gives concordant as well as additional information. Figure 7 shows a perspective view of the complex[39]. The cobalt is bonded to only one of the oxygen atoms of

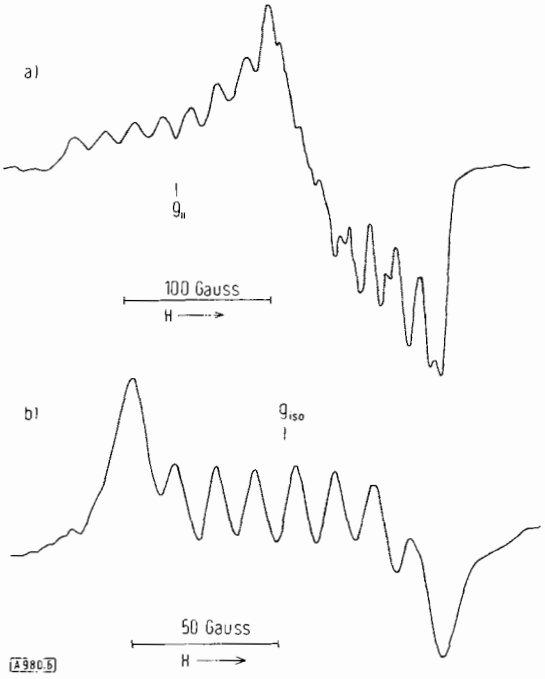


Fig. 6. EPR spectra of Co(acacen)pyO_2; a) frozen toluene solution at 77 K; b) fluid toluene solution at 215 K (after [36]).

the O_2 ligand. Coordination about cobalt is approximately octahedral with the four Schiff base ligand atoms coplanar with the metal atom. The bond angle Co—O—O is 126°, and the O—O distance of 1.26 Å corresponds in fact approximately to that found in a superoxide anion (cf. Table 1).

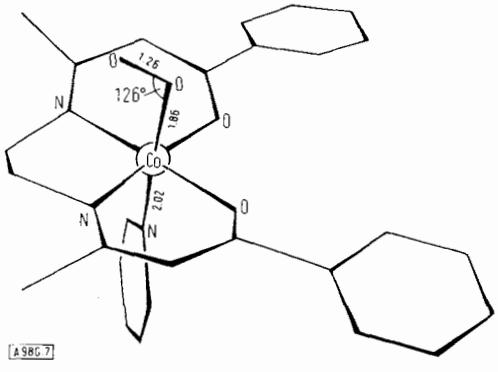
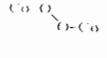
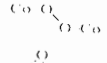


Fig. 7. Perspective view of the mononuclear oxygen complex Co(bzacen)pyO_2 (after [39]).

Table 1. Oxygen-oxygen bond distances.

Compound	Type	Structure	O—O [Å]	Ref.
O_2	free molecule	O=O	1.2074	[41]
KO_2	superoxide	O_2^-	1.28	[41]
H_2O_2	peroxide	O_2^{2-}	1.49	[42]
Co(bzacen)pyO_2 [a]	reversible O_2 complex		1.26	[39]
$[(NH_3)_5Co—O—O—Co(NH_3)_5]^{4+}$	μ-peroxo complex		1.65	[43]
$[(NH_3)_5Co—O—O—Co(NH_3)_5]^{5+}$	oxidized μ-peroxo complex		1.31	[44]
$(O_2)Ir(Cl)(CO)(P(C_6H_5)_3)_2$	reversible O_2 complex		1.30	[45]
$(O_2)Ir(I)(CO)(P(C_6H_5)_3)_2$	irreversible O_2 complex		1.51	[30]

[a] Cf. Fig. 7.

The same arrangement has also been reported for Co(acacen)-pyO_2[40] [Co(acacen) = *(2a)*]. The bent bond C—O—O requires some further comment. The molecular orbitals of O_2 in its "valence state", *i.e.* with the two antibonding π electrons paired under the influence of the field of a transition metal, have been shown in Figure 3. From this picture two natural possibilities for coordination arise, one [*(10)*] in which the metal lies in a lone pair direction, the metal—O—O angle being approximately 120°, and the other [*(11)*] in which the metal lies on the x axis of the O_2 molecule[*], and forms a coordinative double bond comparable with that between transition metals and olefins (M = metal):

(10)   *(11)*

Evidently, the cobalt complexes discussed so far belong to the first type. (Other metals form bonds of the second type, see below.) As soon as the oxygen molecule has approached the transition metal as the sixth ligand, the d-orbital splitting becomes that of an octahedral complex (Fig. 4, right-hand side). A coordinative σ bond is established between one of the oxygen lone pairs and d_{z^2} of cobalt, and there is also a considerable amount of back-donation from one of the doubly occupied d-orbitals of the cobalt to the antibonding empty $1\pi_g(p_x)$ of the oxygen molecule. This latter back-bonding weakens the O—O bond, as evidenced by the bond distance, 1.26 Å (cf. Table 1).

The binuclear cobalt-oxygen complexes $[(NH_3)_5Co—O—O—Co(NH_3)_5]^{4+}$ and L(Co(salen))—O—O—(Co(salen))L (L = dimethylformamide) have also been investigated by X-ray structural analysis. They possess bent Co—O—O—Co bonds, with Co—O—O bonds angles of 112°[43] and 120.4°[15] respectively (see Fig. 8).

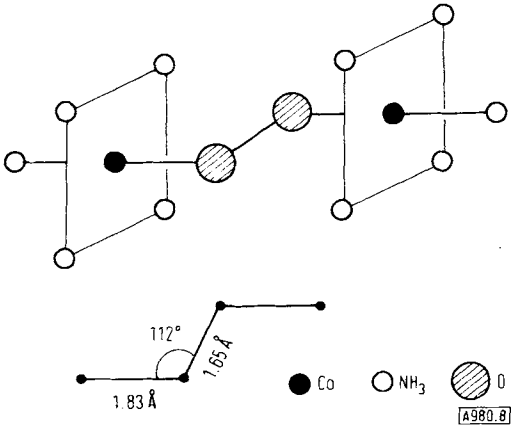


Fig. 8. Structure of $[(NH_3)_5CoO_2Co(NH_3)_5]^{4+}(SCN)_4$ (after [43]).

Interestingly, these binuclear cobalt-oxygen complexes are diamagnetic, whereas the parent compounds, *e.g.* $[(NH_3)_6Co]^{2+}$ or Co^{II}(salen), are paramagnetic (low spin d^7, one unpaired electron). If again we assume that the unpaired electrons of the free oxygen molecule are paired in one of the $1\pi_g$ orbitals under the influence of the cobalt neighbors, the diamagnetism of the complex implies that the unpaired electrons of the two cobalt centers are now paired in a four-center molecular orbital embracing Co—O—O—Co. This hypothesis finds experimental corroboration by EPR: The complex $[(NH_3)_5CoO_2Co(NH_3)_5]^{4+}$ can easily be oxidized to $[(NH_3)_5CoO_2Co(NH_3)_5]^{5+}$. The latter is paramagnetic (one unpaired electron), and has a 15-line EPR signal[46], showing the interaction of the unpaired electron with two identical Co nuclei (^{59}Co: $I = 7/2$). Similar EPR spectra have been found with other oxidized oxygen-bridged Co complexes[18,47,48]. A particularly well resolved signal was observed[48] when the binuclear oxygen complex of bis(histidinato)cobalt(II) *(7)* was oxidized with Ce^{4+} (see Fig. 9).

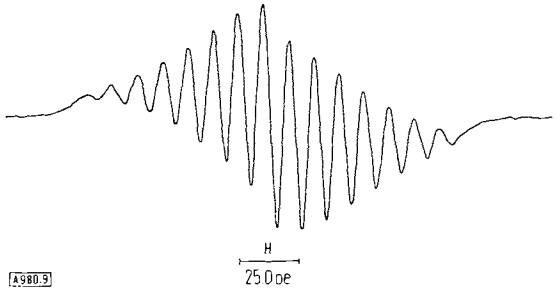


Fig. 9. EPR spectrum of the binuclear oxygen complex of bis(histidinato)-cobalt(II) *(7)* (after [48]).

These spectra show that the unpaired electron moves in fact in a molecular orbital including the two cobalt nuclei in a symmetric way. A proposal for the four center MO is given in Figure 10. The four centers are held together by a π bond between the empty antibonding π orbital of the oxygen, $1\pi_g(p_x)$, and two doubly occupied d-orbitals of the two cobalts. This type of bonding brings spin density into the antibonding π orbital of the oxygen molecule and thus weakens the bond. From the relatively small EPR coupling constant, $a_{Co} \approx 12$ gauss, it can be concluded that the four-center MO is mostly localized on the O—O part of the complex. This is in agreement with the O—O bond distance found for the oxidized complex (see Table 1), which is similar to that of a superoxide, O_2^-.

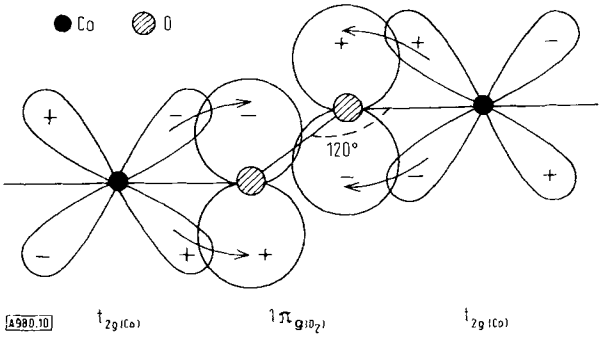


Fig. 10. Four-center molecular orbital in $[(NH_3)_5Co—O—O—Co(NH_3)_5]^{4+}$ and similar complexes (after [4]).

The bent Co—O—O—Co bond indicates that there is also σ interaction between a lone pair on each oxygen atom and vacant $d(e_g)$ orbitals of the metal on either side.

The original diamagnetic complexes, such as $[(NH_3)_5CoO_2Co(NH_3)_5]^{4+}$, on the other hand, may be assumed to have two electrons in this same four-center orbital, making the O—O part then similar to a peroxide ion, O_2^{2-}. In fact the O—O bond distance is large, even somewhat larger than in a peroxide (see Table 1).

[*] The coordinate systems for the oxygen molecule and the transition metal center are independent.

Although it is customary to designate these bridge-bonded, binuclear cobalt-oxygen complexes as μ-superoxo- and μ-peroxo-cobalt(III) complexes, it should be born in mind that the assignment of integral oxidation numbers is not correct (EPR evidence). It was suggested[7] that the term metal-oxygen complex should apply to all relevant species containing a complexed O_2 moiety, as is customary with the analogous metalnitrogen complexes.

Vaska's oxygen complex $Ir(Cl)(CO)(P(C_6H_5)_3)_2O_2$ (see Section 2.2), and some related complexes of iridium and rhodium, have the oxygen molecule bonded symmetrically. X-Ray studies[30, 45, 49, 50] have revealed equal distances between the metal and either of the two oxygen atoms; the arrangement of the ligands is trigonal-bipyramidal, with the phosphanes situated at the apices (see Fig. 11). The symmetric position of the two oxygen atoms suggests a bonding [*(11)*] similar to that of the Dewar-Chatt model for the metal-olefin complexes[51, 52]. A σ bond is formed between the filled bonding π orbital of the oxygen and an empty d orbital of the metal. Back donation occurs, to off-set the resultant dipole, from a filled d orbital to the antibonding $1\pi_g$ orbital of the O_2.

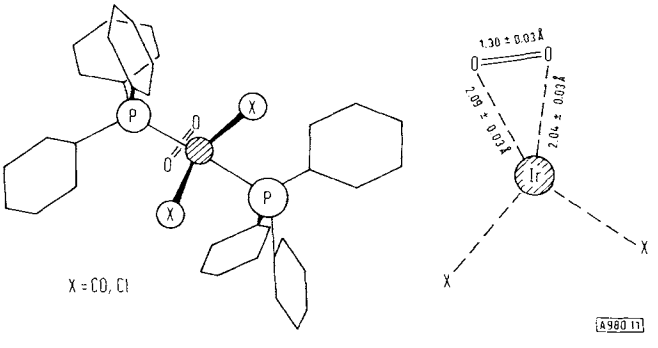


Fig. 11. Structure of $IrO_2(CO)(Cl)(P(C_6H_5)_3)_2$ (after [45] and [4]).

Presumably the π bonding predominates in transition metal-oxygen complexes. This is indicated by the observation that higher electron density at the metal center favors complex formation. Thus, as the electronegativity of the halide in the iridium complex (Fig. 11) decreases (Cl > I), the strength of the bonding of the oxygen molecule to the metal increases (see Table 1; note that in the iodide complex the O_2 is irreversibly bound). At the same time, the O—O bond is destabilized, *i. e.* the bond length is increased, indicating the higher electron density in the antibonding π orbital.

Variation of the donor strength of the phosphane ligand (cf. Fig. 11) has concordant consequences: the better the donor $[(p\text{-}ClC_6H_4)_3P < (C_6H_5)_3P < (p\text{-}CH_3C_6H_4)_3P < (p\text{-}CH_3OC_6H_4)_3P]$ the higher the rate of oxygen uptake, and the greater the stability of the oxygen complex[53].

The importance of π bonding in metal-oxygen complexes is also reflected in the observation that d^{10} metals, which do not possess empty d-orbitals, also form complexes with O_2 but not with H_2[54].

After the discussion of the different modes of attachment of the oxygen molecule to the metal center, the question may arise how the oxygen is bonded in the natural oxygen carriers such as hemoglobin or myoglobin. The macromolecular character of these compounds makes a direct X-ray determination of the geometry of the oxygen unlikely. The bent-bonding mode, as well as the symmetric attachment are able to provide reversibility (cf. Section 2), and in this sense both could be models for the natural compounds. Thus one may ask which molecular properties are decisive for the type of bonding. For energetic reasons the symmetric attachment should always be favored since the bonding π-MO of O_2 is estimated[35] to have a smaller ionization potential than the lone pair orbitals. It was suggested by *Mingos*[55] that the complex is forced into the bent-bonding mode whenever the highest occupied metal orbital has a symmetry different from that of the oxygen acceptor orbital $1\pi_g$[*]. The latter is a π orbital; in the cobalt complexes discussed above the donating orbital is d_{z^2}, a σ orbital (cf. Fig. 4, center). In the square planar d^8 complexes of Ir^I and Rh^I, on the other hand, the highest occupied orbital is d_{xy} (2 electrons), which has π symmetry.

From this point of view the bonding of O_2 to the iron(II) center in hemoglobin should be expected to be of the symmetric type. Although the ligand arrangement is similar to that in the cobalt(II) complexes, it has to be taken into account that one electron less has to be placed into the MO energy diagram (Fig. 4, center), the highest occupied orbital then being d_{xy}, which is a π orbital in this symmetry.

4. Reactions of Coordinated Oxygen

The X-ray crystallographic studies of the synthetic transition metal-oxygen complexes discussed in the preceding section have indicated that a certain activation of the oxygen molecule takes place upon coordination, as shown by an elongation of the O—O bond. This suggests the use of the activated oxygen for specific oxidation reactions, not possible with free gaseous oxygen. In fact, several cases of homogeneous catalysis of hydrocarbon autoxidation and epoxidation with oxygen complexes have been reported[56]. It appears, however, that most or all of these reactions have the characteristics of radical chain processes[57]. The transition metal catalyzes the decomposition of peroxides, as does Co-naphthenate. This kind of oxidation, which is generally very unspecific and gives a large amount of acidic by-products, will not be treated here.

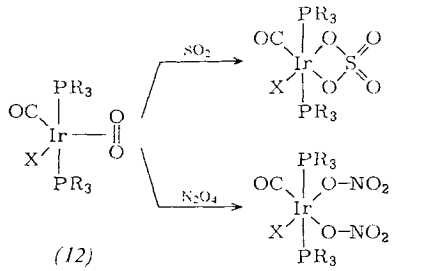
The desired specific oxidation of substrate would require simultaneous coordination of oxygen and substrate molecule to the same metal center prior to reaction. In the case of olefins, only a non-catalytic reaction of this type has been achieved up to now. In several cases, however, the catalytic oxidation of phosphane, carbon monoxide, or isocyanide ligands has been reported.

4.1. Non-Catalytic Reactions

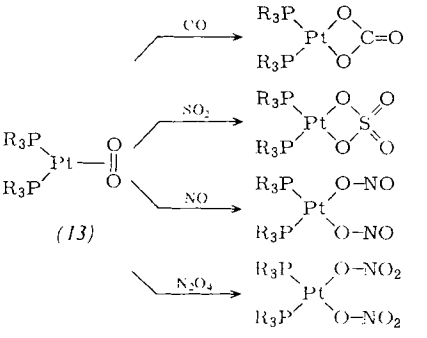
The stoichiometric oxidation of SO_2, CO, CO_2, NO, and N_2O_4 has been repeatedly observed, particularly with $IrX(CO)(O_2)(P(C_6H_5)_3)_2$ *(12)*[58], $PtO_2(P(C_6H_5)_3)_2$ *(13)*[54, 59] (X = Cl, Br, I), and with $NiO_2(t\text{-}BuNC)_2$ *(14)*[60].

These reactions involve an increase of the formal valency state of the metal, together with the formation of a stable anion (or two anions) attached to the metal:

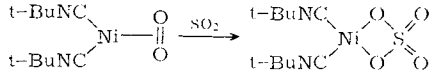
[*] This was concluded from considerations based on an approximate form of the second order Jahn-Teller effect [55].



(12)



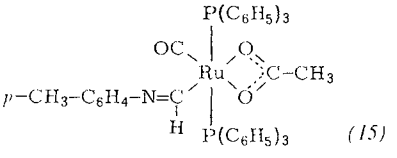
(13)



(14)

R = C_6H_5

An unusual reaction of this type was found when $Ru(O_2)(CO)(CN\text{-}p\text{-}CH_3C_6H_4)(P(C_6H_5)_3)_2$ was heated in ethanol: the alcohol is oxidized to coordinated acetate, and a hydride ion of the alcohol is donated to the *p*-tolyl isocyanide ligand, forming the uncommon formimidoyl ligand[61]:



(15)

When the acetate ligand is cleaved from (15) by iodide, hydride moves to the metal, and the original isocyanide ligand is regenerated in $RuHI(CO)(CN\text{-}p\text{-}CH_3C_6H_4)(P(C_6H_5)_3)_2$. This hydride may react with excess of acetate, the hydride returning to the isocyanide.

The oxidation of primary amine ligand to nitrile and of methylamine to cyanide has been achieved with the corresponding hexakis(amine)ruthenium(II) ion under a slight oxygen pressure[62].

The first case of oxidation of a hydrocarbon with molecular oxygen at a transition metal center under mild conditions appears to be the rhodium(I)-promoted oxidation of a terminal olefin (1-hexene) to a ketone (2-hexanone)[63]. A free radical type of reaction has been excluded. Although the yield is small (some 20—30%, referred to the metal), this reaction is remarkable. If $RhCl(P(C_6H_5)_3)_3$ (16) is brought together with O_2 at ambient temperature in benzene solution, two of the three phosphane ligands are oxidized to phosphane oxide (see Fig. 12, reaction sequence on the left-hand side). If olefin is present it appears able to compete with a phosphane ligand P for a coordination site, and becomes oxygenated instead of one of the phosphane ligands. It appears to be significant that the system provides an acceptor (the phosphane) for one of the oxygen atoms.

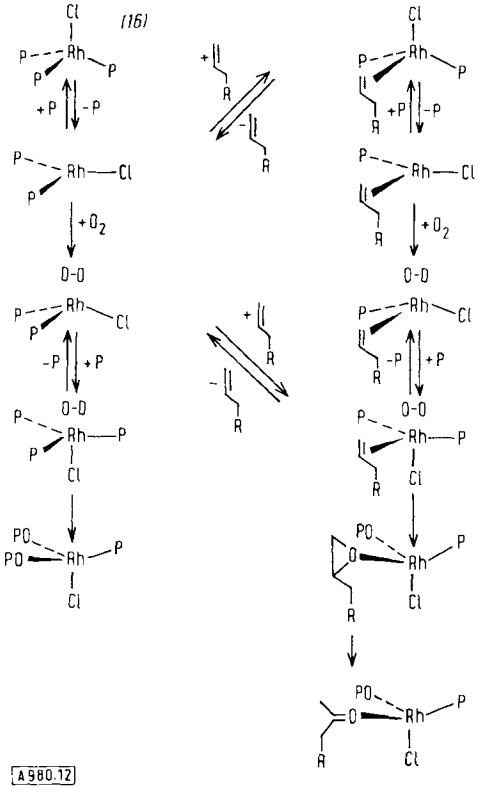


Fig. 12. Rhodium(I)-catalyzed oxidation of 1-hexene to 2-hexanone. The phenyl groups of the phosphane and phosphane oxide ligands have been omitted; R = *n*-C_3H_7 (according to [63]).

4.2. Catalytic Reactions

Triphenylphosphane is oxidized to triphenylphosphane oxide by several transition metal-oxygen complexes. Thus, *Wilke et al.*[32] found that $M(P(C_6H_5)_3)_4$ (M = Ni(0), Pd(0); Pt(0)) react with oxygen, in benzene or toluene solution, to give the complex $M(P(C_6H_5)_3)_2O_2$. At elevated temperature (with M = Pd, Pt at $T > 90$ °C, with M = Ni already at $T > -35$ °C) the oxygenated complex decomposes to metal and two molecules of phosphane oxide. In the presence of an excess of phosphane, the metal may be scavenged, regenerating the starting complex, *i.e.* the process becomes catalytic. With the Ni(0) compound some 50 mol of phosphane have been oxidized per mol of Ni complex; with Pd(0) a turnover of at least 500 was obtained.

The mechanism of this reaction has been studied, for the case of Pt(0), by *Halpern et al.*[64,65] on the basis of optical absorption spectroscopy and kinetic measurements. A solution of $Pt(P(C_6H_5)_3)_4$ in benzene exhibits strong absorptions in the range 400—560 nm. The same absorptions, with identical intensity, are observed when ethylene is displaced from the complex $Pt(P(C_6H_5)_3)_2(C_2H_4)$ (at the same Pt concentration), by adding $P(C_6H_5)_3$ in the ratio 1:1. It is convincingly concluded that the predominant species in both cases is $Pt(P(C_6H_5)_3)_3$. Therefore, the first step in the mechanism of the catalytic oxidation of the phosphane with $Pt(P(C_6H_5)_3)_3$ is assumed to be:

$$PtP_4 \rightarrow PtP_3 + P \qquad (7)$$

(The phenyl groups have been omitted in this and the following equations.)

The subsequent reaction sequence has been established investigating the two component reactions separately:

$$PtP_3 + O_2 \xrightarrow{k_1} PtP_2O_2 + P \quad (8)$$

$$PtP_2O_2 + P \xrightarrow{k_2} PtP_3O_2 \xrightarrow[fast]{2P} PtP_3 + 2PO \quad (9)$$

Each reaction was followed spectrometrically by monitoring the concentration of $Pt(P(C_6H_5)_3)_3$ in the region mentioned above. Reaction (8) was studied under conditions ensuring minimum interference from reaction (9) ($[O_2] \ll [Pt]$). The kinetic experiments on reaction (9) were performed by adding a large excess of $P(C_6H_5)_3$ to a benzene solution of $Pt(P(C_6H_5)_3)_2O_2$, and spectrometrically measuring the formation of $Pt(P(C_6H_5)_3)_3$. The resulting rate laws are[65]:

$$-d[PtP_3]/dt = k_1[PtP_3][O_2] \quad (10)$$

$$+d[PtP_3]/dt = k_2[PtP_2O_2][P] \quad (11)$$

with $k_1 = 2.61\ mol^{-1}\ s^{-1}$ and $k_2 = 0.151\ mol^{-1}\ s^{-1}$, at 25°C. The mechanism was further checked under conditions such that both reactions are occurring simultaneously, *i.e.* with a large excess of $P(C_6H_5)_3$, with constant O_2 pressure, and measuring the rate of consumption of oxygen:

$$-d[O_2]/dt = k_1[PtP_3][O_2] \quad (12)$$

Assuming stationary state conditions:

$$d[PtP_3]/dt = k_1[PtP_3][O_2] - k_2[PtP_2O_2][P] = 0 \quad (13)$$

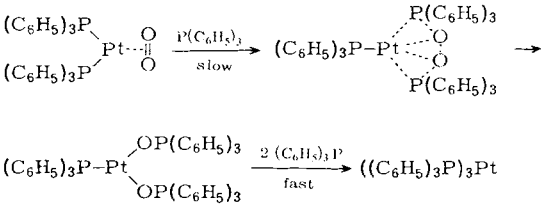
and making use of the conservation relation

$$[PtP_3] + [PtP_2O_2] = [Pt]_{total} \quad (14)$$

the rate law for the oxygen consumption is:

$$-\frac{d[O_2]}{dt} = \frac{k_1 k_2 [Pt]_{total}[P][O_2]}{k_1[O_2] + k_2[P]} \quad (15)$$

Perfect agreement between the measured rate of O_2 uptake and values calculated from eq. (14) with the rate constants given above, lends strong support to the assumed reaction sequence, eqs. (8) and (9)[65]. However, the detailed mechanism of the individual steps, particularly of the transformation of the phosphane into the phosphane oxide at the metal center, is not elucidated from these kinetic data. Intuitively, *Halpern et al.* interpreted this step in terms of a "dissociative insertion" reaction [eq. (16)].



$$(C_6H_5)_3P-Pt(OP(C_6H_5)_3)_2 \xrightarrow[fast]{2\,(C_6H_5)_3P} ((C_6H_5)_3P)_3Pt + 2\,(C_6H_5)_3PO \quad (16)$$

Other complexes which have been reported to catalytically oxidize triphenylphosphane to the oxide include $Ru(O_2)(NCS)(NO)(P(C_6H_5)_3)_2$[66], for which a similar reaction mechanism with "dissociative oxygen insertion" has been suggested; furthermore $RuCl_2(P(C_6H_5)_3)_3$[67], which is relatively active, converting 10 mol of $P(C_6H_5)_3$ into $OP(C_6H_5)_3$ per mol of Ru complex in 15 min at 20°C, and *Vaska*'s complex, $IrX(CO)(P(C_6H_5)_3)_2$[68][*] which was, however, found to be reactive only at elevated temperature (110°C, turnover 4—5 in 9 h).

An interesting simultaneous catalytic (although slow) oxidation of phosphane to phosphane oxide, and of CO to CO_2, was achieved by exposing $RhCl(CO)(P(C_6H_5)_3)_2$ to a slight pressure of CO and O_2 at 100°C[70].

The catalytic oxidation of *tert*-butyl isocyanide to the corresponding isocyanate has been observed with the complex $((CH_3)_3CNC)_2NiO_2$ *(14)*, at room temperature[71].

Finally, a ligand reaction has also been found for binuclear metal-oxygen complexes, namely $X_2(RNH_2)_3Co—O—O—Co(RNH_2)_3X_2$, with X = organic anion, *e.g.* acetate, and R = organic group, *e.g.* propyl[72]. The complexes are formed if the organic cobalt salt is dissolved in the amine, and oxygen is introduced into the solution. They are diamagnetic, irreversible, and soluble in alcohols or dimethylformamide. Thermolysis of the dry complexes leads to a homopolar cleavage of the O—O bond with subsequent radical reactions involving amine ligand. In the case of R = propyl, the main products are allylamine and dipropylamine. It is suggested that the primary radical formation by cleavage of the O—O bond is followed by the dehydrogenation of the propyl groups. The resulting allylic groups exhibit weak C—N (75.2 kcal/mol) and C—H bonds (82.5 kcal/mol[73]). Radical cleavage of these bonds leads to the observed alkylation of the primary amine. After the thermolysis the cobalt is present as paramagnetic, mononuclear Co^{II}. It dissolves in fresh amine and the resulting solution takes up oxygen at essentially the same rate as during the first oxygenation; thermolysis leads to the same products (catalysis).

5. Outlook

The transition metal-oxygen complexes may be divided into four classes, with different properties, reaction patterns, and prospects for the future.

Reversible oxygen complexes: This group includes all models for the natural oxygen carriers. Although much has already been elucidated concerning the bonding in such complexes, the actual mode of fixation of the oxygen to the metal in the natural complexes still remains a matter of speculation (cf. Section 3.2).

Stable oxygen complexes: Although interesting in themselves as regards bond lengths, bond angles, and symmetry properties, this category does not yet present any prospects for practical use. The situation here is similar to that in the field of transition metal-nitrogen complexes: the isolable stable complexes do not appear to be suitable for catalysis (see, *e.g.* [74]).

[*] The catalytic oxidation of styrene to benzaldehyde at 110°C with *Vaska*'s complex was also reported [68]. However, no effort was made to exclude a radical mechanism. The free radical alternant copolymerization of styrene and O_2 is well established [69]; the copolymer decomposes at elevated temperature to benzaldehyde and formaldehyde.

Complexes with oxidized ligands: This group might, in some cases, be of interest for synthetic purposes. Free oxygen would not react under mild conditions with SO_2, CO, NO, N_2O_4; some of the metal-oxygen complexes, however, transform these substrates easily to oxidized, anionic ligands. Since the latter are generally more strongly bonded to the metal than the starting material, the reaction stops there, and no catalysis is to be expected (Section 4.1).

Complexes that catalytically oxidize ligands: Evidently catalysis is possible only if the oxidized ligand is easily displaced by substrate molecules. Although present knowledge is still far away from a specific catalytic oxidation of certain substrates, particularly olefins, some progress has already been achieved (Section 4.2).

Obviously, the first and fourth classes are the most interesting from the point of view of catalysis, in the sense of oxygen transport as well as for oxidations of practical interest. At the present it is not yet possible to predict which complex will perform which task, but the problem should perhaps not be seen isolated. It may be expected that the investigation of bonding and ligand influences within different types of complexes (with O_2, N_2, CO, olefins, diolefins, *etc.*) will prove mutually stimulating, and will provide a better insight into possibilities and limitations of homogeneous catalysis with transition metal complexes.

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[1] See, *e.g., C. R. Adams*, Ind. Eng. Chem. *61*, 30 (1969).

[2] *E. Fremy*, Liebigs Ann. Chem. *83*, 227, 289 (1852).

[3] *L. H. Vogt, H. M. Faigenbaum*, and *S. E. Wiberley*, Chem. Rev. *63*, 269 (1963).

[4] *E. Bayer* and *P. Schretzmann*, Struct. Bonding *2*, 181 (1967).

[5] *A. G. Sykes* and *J. A. Weil*, Progr. Inorg. Chem. *13*, 1 (1970).

[6] *R. G. Wilkins*, Advan. Chem. Ser. *100*, 111 (1971).

[7] *V. J. Choy* and *C. J. O'Connor*, Coord. Chem. Rev. *9*, 145 (1972).

[8] *J. S. Valentine*, Chem. Rev. *73*, 235 (1973).

[9] *A. E. Martell* and *M. Calvin*: Chemistry of Metal Chelate Compounds. Prentice Hall, New York 1953.

[10] *M. Calvin, R. H. Bailes*, and *W. K. Wilmarth*, J. Amer. Chem. Soc. *68*, 2254 (1946).

[11] *H. Diehl*, Iowa State Coll. J. Sci. *22*, 271 (1946).

[12] *C. Floriani* and *F. Calderazzo*, J. Chem. Soc. *A 1969*, 946.

[13] *C. Busetto, C. Neri, N. Palladino*, and *E. Perrotti*, Inorg. Chim. Acta *5*, 129 (1971).

[14] *D. Diemente, B. M. Hoffman*, and *F. Basolo*, Chem. Commun. *1970*, 467.

[15] *M. Calligaris, G. Nardin*, and *L. Randaccio*, Chem. Commun. *1969*, 763.

[16] *A. L. Crumbliss* and *F. Basolo*, J. Amer. Chem. Soc. *92*, 55 (1970).

[17] *J. D. Duncan, L. M. Engelhardt, M. Green*, and *P. A. Tasker*, The Chemical Society Autumn Meeting 1971, York, UK; Preprints B 26.

[18] *G. N. Schrauzer* and *L. P. Lee*, J. Amer. Chem. Soc. *92*, 1551 (1970).

[19] *E. W. Abel, J. M. Pratt*, and *R. Whelan*, Chem. Commun. *1971*, 449.

[20] *J. Z. Hearon, D. Burk*, and *A. L. Schade*, J. Nat. Cancer Inst. *9*, 337 (1949).

[21] *J. Simplicio* and *R. G. Wilkins*, J. Amer. Chem. Soc. *89*, 6092 (1967).

[22] *A. Werner* and *A. Mylius*, Z. Anorg. Chem. *16*, 245 (1898).

[23] *S. Fallab*, Z. Naturwiss.-Med. Grundlagenforsch. *2*, 220 (1965); Chimia *21*, 538 (1967).

[24] *S. Fallab*, Chimia *23*, 177 (1969).

[25] *F. Miller* and *R. G. Wilkins*, J. Amer. Chem. Soc. *92*, 2687 (1970).

[26] *F. Miller, J. Simplicio*, and *R. G. Wilkins*, J. Amer. Chem. Soc. *91*, 1962 (1969).

[27] *A. Zuberbühler, T. Kaden*, and *F. Koechlin*, Helv. Chim. Acta *54*, 1502 (1971).

[28] *B. Erdem* and *S. Fallab*, Chimia *19*, 463 (1965).

[29] *L. Vaska*, Science *140*, 809 (1963).

[30] *J. A. McGinnety, N. C. Payne*, and *J. A. Ibers*, J. Amer. Chem. Soc. *91*, 6301 (1969).

[31] *M. M. Taqui Khan, R. K. Andal*, and *P. T. Manoharan*, Chem. Commun. *1971*, 561.

[32] *G. Wilke, H. Schott*, and *P. Heimbach*, Angew. Chem. *79*, 62 (1967); Angew. Chem. internat. Edit. *6*, 92 (1967).

[33] *A. W. Addison* and *R. D. Gillard*, J. Chem. Soc. *A 1970*, 2523.

[34] *F. A. Cotton* and *G. Wilkinson*: Advanced Inorganic Chemistry. Interscience Publ., New York 1966.

[35] *J. S. Griffith*, Proc. Roy. Soc. *A 235*, 23 (1956).

[36] *B. M. Hoffman, D. L. Diemente*, and *F. Basolo*, J. Amer. Chem. Soc. *92*, 61 (1970).

[37] See, *e.g., M. C. Day* and *J. Selbin*: Theoretical Inorganic Chemistry. Reinhold, New York 1962.

[38] *E. I. Ochiai*, J. C. S. Chem. Comm. *1972*, 489.

[39] *G. A. Rodley* and *W. T. Robinson*, Nature *235*, 438 (1972).

[40] *M. Calligaris, G. Nardin, L. Randaccio*, and *G. Tauzher*, Inorg. Nucl. Chem. Lett. *9*, 419 (1973).

[41] *S. C. Abraham*, Quart. Rev. Chem. Soc. *10*, 407 (1956).

[42] *S. C. Abrahams, R. L. Collin*, and *W. N. Lipscomb*, Acta Crystallogr. *4*, 15 (1951).

[43] *N. G. Vannerberg*, Acta Crystallogr. *18*, 449 (1965).

[44] *W. P. Schaefer* and *R. E. Marsh*, Acta Crystallogr. *16*, 247 (1963).

[45] *S. J. La Placa* and *J. A. Ibers*, Science *145*, 920 (1964); J. Amer. Chem. Soc. *87*, 2581 (1965).

[46] *E. A. V. Ebsworth* and *J. A. Weil*, J. Phys. Chem. *63*, 1890 (1959).

[47] *M. Mori, J. A. Weil*, and *J. K. Kinnaird*, J. Phys. Chem. *71*, 103 (1967).

[48] *J. A. Weil* and *J. K. Kinnaird*, Inorg. Nucl. Chem. Lett. *5*, 251 (1969).

[49] *J. A. McGinnety, R. J. Doeders*, and *J. A. Ibers*, Inorg. Chem. *6*, 2243 (1967).

[50] *M. S. Weininger, I. F. Taylor*, and *E. L. Amma*, Chem. Commun. *1971*, 1172.

[51] *M. J. S. Dewar*, Bull. Soc. Chim. Fr. *18*, C 17 (1951).

[52] *J. Chatt*, J. Chem. Soc. *1953*, 2939.

[53] *L. Vaska* and *L. S. Chen*, Chem. Commun. *1971*, 1080.

[54] *J. P. Collman*, Accounts Chem. Res. *1*, 136 (1968).

[55] *D. M. P. Mingos*, Nature Phys. Sci. *230*, 154 (1971); *229*, 193 (1971).

[56] See, *e.g., J. Blum, H. Rosenman*, and *E. D. Bergmann*, Tetrahedron Lett. *1967*, 3667; *A. J. Bird* and *G. R. S. Subba Rao*, *ibid. 1968*, 2917; Brit. Pat. 1 199 387; *K. Takao, M. Wayaku, Y. Fujiwara, T. Imanaka*, and *S. Teranishi*, Bull. Chem. Soc. Jap. *43*, 3898 (1970).

[57] *E. W. Stern*, Chem. Commun. *1970*, 736, and other papers cited therein.

[58] *R. W. Horn, E. Weissberger*, and *J. P. Collman*, Inorg. Chem. *9*, 2367 (1970).

[59] *J. P. Collman, M. Kubota*, and *J. Hosking*, J. Amer. Chem. Soc. *89*, 4809 (1967).

[60] *S. Otsuka, A. Nakamura, Y. Tatsunu*, and *M. Miki*, J. Amer. Chem. Soc. *94*, 3761 (1972).

[61] *D. F. Christian, G. R. Clark, W. R. Roper, J. M. Waters*, and *K. R. Whittle*, J. C. S. Chem. Comm. *1972*, 458.

[62] *W. R. McWhinnie, J. D. Miller, J. B. Watts*, and *D. Y. Waddan*, Chem. Commun. *1971*, 629.

[63] *C. Dudley* and *G. Read*, Tetrahedron Lett. *52*, 5273 (1972).

[64] *J. P. Birk, J. Halpern*, and *A. L. Pickard*, J. Amer. Chem. Soc. *90*, 4491 (1968).

[65] *J. Halpern* and *A. L. Pickard*, Inorg. Chem. *9*, 2798 (1970).

[66] *B. W. Graham, K. R. Laing, C. J. O'Connor*, and *W. R. Roper*, J. C. S. Dalton *1972*, 1237.

[67] *S. Cenini, A. Fusi*, and *G. Caparella*, Inorg. Nucl. Chem. Lett. *8*, 127 (1972).

[68] *K. Takao, Y. Fujiwara, T. Imanaka*, and *S. Teranishi*, Bull. Chem. Soc. Jap. *43*, 1153 (1970).

[69] *G. Henrici-Olivé* and *S. Olivé*, Makromol. Chem. *24*, 64 (1957).

[70] *J. Kiji* and *J. Furukawa*, Chem. Commun. *1970*, 977.

[71] *S. Otsuka, A. Nakamura*, and *Y. Tatsuno*, Chem. Commun. *1967*, 836.

[72] *G. Henrici-Olivé* and *S. Olivé*, J. Organometal. Chem. *52*, C49 (1973).

[73] *K. W. Egger* and *A. T. Cocks*, Helv. Chim. Acta *56*, 1537 (1973).

[74] *G. Henrici-Olivé* and *S. Olivé*, Angew. Chem. *81*, 679 (1969); Angew. Chem. internat. Edit. *8*, 650 (1969).

Electronic Transitions in Transition Metal Compounds at High Pressure

By H. G. Drickamer[*]

Very high pressure is becoming increasingly important for investigating electronic structure. The relative shift in energy of electronic orbitals which is commonly observed at high pressure can frequently lead to a new ground state for the system. These electronic transitions may result in changes in electrical, optical, or magnetic properties as well as changes in chemical reactivity. Electronic transitions in metals and insulator-metal transitions have been widely studied by physicists. Recently, it has been found that electronic transitions in aromatic hydrocarbons and their electron donor-acceptor complexes can induce chemical reactivity and lead to the formation of new classes of hydrocarbons.

Electronic transitions in transition metal complexes may lead to changes in spin state; both increase and decrease in multiplicity with increasing pressure have been observed. In addition, it has been shown that Fe(III) and Cu(II) reduce at high pressure in a variety of compounds. The behavior of these transition metal ions is described in some detail in relation to the general area of high pressure and electronic structure.

1. Introduction

Over the past two decades it has become apparent that very high pressure is a powerful tool for studying electronic structure. Its application first became common in solid state physics and geophysics, but has more recently been extended to physical, inorganic, and organic chemistry.

The pioneering work of *Bridgman*[1] provided techniques for studies at up to 12 kbars (1 kbar = 987 atmospheres), and in some cases up to 30 kbars, using hydrostatic media. These techniques have been applied to many problems of solid state physics, as well as to investigations on the physical chemistry of solutions[2], relaxation processes in solution[3], electronic and molecular spectroscopy[4], and also to the study of organic reaction mechanisms[5, 6].

In addition, *Bridgman* developed techniques for electrical resistance and pressure-volume measurements utilizing quasihydrostatic media at 70 kbars or above. In the past fifteen years the static pressure range has been extended to several hundred kilobars. More important—measurements such as optical absorption and emission and Mössbauer resonance which are sensitive to electronic structure are now possible.

In this review we discuss studies of transition metal ions in this high pressure range. In order to place these investigations in their proper context a brief review of the general effects of pressure on electronic structure will first be given. The experimental techniques have been covered in detail elsewhere[7–9] and will not be discussed here. There exist reviews[9–13] with extensive references to the literature on high pressure and electronic structure. We list here primarily very recent references, or those not included in the above literature. In general we express energies in electron volts and optical peak locations in cm^{-1} or kilokaysers (one eV per atom $\hat{=}$ 23 kcal per g-atom $\hat{=}$ 8000 cm^{-1} = 8.0 kK).

From our viewpoint the primary effect of compression is to increase overlap of adjacent electronic orbitals. A very general consequence of this increased overlap is the relative shift in energy of one type of orbital with respect to another. Since orbitals of different quantum number differ in radial extent, or in orbital shape (angular momentum) or in compressibility, this *relative shift in energy* is not surprising. Under many circumstances there may be an excited state which lies not too far in energy above the ground state so that the pressure-induced shift may be sufficient to establish a new ground state for the system, or greatly to modify the characteristics of the ground state by change in configurational interaction. This event we call an electronic transition, which may occur discontinuously at a definite pressure or over a range of pressures, and may have a variety of physical and chemical consequences. We discuss first (Section 2) the kinds of shifts in orbital energy which have been observed, and second (Section 3), the variety of electronic transitions. In both cases strong emphasis is on events relevant to transition metal chemistry.

2. Shifts of Energy Levels

The early high-pressure optical measurements concerned themselves in large part with studies of the change in the gap between the top of the valence band and the bottom of the conduction band[9–11], in insulators or semiconductors. For many substances this gap decreases rapidly with increasing pressure leading ultimately to metallic conductivity in such materials as iodine and higher acenes (*e.g.* pentacene). For materials like germanium, gallium arsenide, and zinc sulfide with complex band structure the gap may actually increase at low pressure.

Other studies include the behavior of color centers in alkali halides[9, 11], transitions from the $4f^n$ to the $4f^{n-1}5d$ configuration in rare earth ions[14], excitations among 3d configurations in transition metal ions[9–13], excitations from π to π^* states in aromatic hydrocarbons and related heterocyclic compounds[9, 11] including aromatic ligands in transition metal complexes, and electron donor-acceptor excitations in both molecular complexes and transition metal complexes[9–13]. We discuss in more detail those types of excitations of particular interest to coordination chemistry.

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2.1. d-d Excitations

The interesting properties of transition metal ions center around the number and arrangement of electrons in the partially filled d shell. In the free ion the five orbitals are degenerate, and, in accordance with Hund's rule, the electrons are arranged to give maximum multiplicity in the ground state. Excited states with partially or completely paired spins lie higher in energy because of the increased interelectronic repulsion associated with spin pairing. The interelectronic repulsion is most conveniently expressed in terms of the Racah parameters B and C, which we take here to be empirically determined. When the ion is placed in a crystal lattice, or in a complex, the fivefold degeneracy is partially removed, as orbitals of different symmetry are affected differently by the nearest neighbor atoms or ions (the ligands). For instance, in an octahedral complex (six neighbors), the D_{z^2} and $d_{x^2-y^2}$ orbitals of $E_g(\sigma)$ symmetry are increased in energy relative to the d_{xy}, d_{yz}, and d_{xz} orbitals of $T_{2g}(\pi)$ symmetry. This splitting (Δ) is a measure of the field due to the ligands. In molecular orbital language the splitting is between the antibonding E_g orbitals and the essentially nonbonding T_{2g} orbitals.

In most complexes the electrons are still arranged in a high spin configuration because the spin pairing repulsion is larger than the potential energy necessary to occupy the T_{2g} orbitals. If the ligand field Δ is sufficiently large the potential energy effect may more than compensate for the interelectronic repulsion, and a low spin configuration results. In low spin systems the ligands usually have low lying states of π symmetry which are empty and can bond with the metal d_π orbitals. This "back-donation" of metal electrons into ligand orbitals stabilizes the d_π orbitals and so gives the large value of Δ. Thus the 3d electrons tend to be delocalized in low spin complexes. Molecules of lower symmetry such as metalloporphyrins or phthalocyanines may exhibit intermediate spin or mixed spin states.

For high spin complexes the ligand field increases with increasing pressure. A simple point charge model would predict $\Delta \sim R^{-5} \sim \rho^{5/3}$, where R is the metal ion—ligand distance and ρ is the density. Figure 1 compares the measured values of Δ for NiO with the prediction (solid line) from density data.

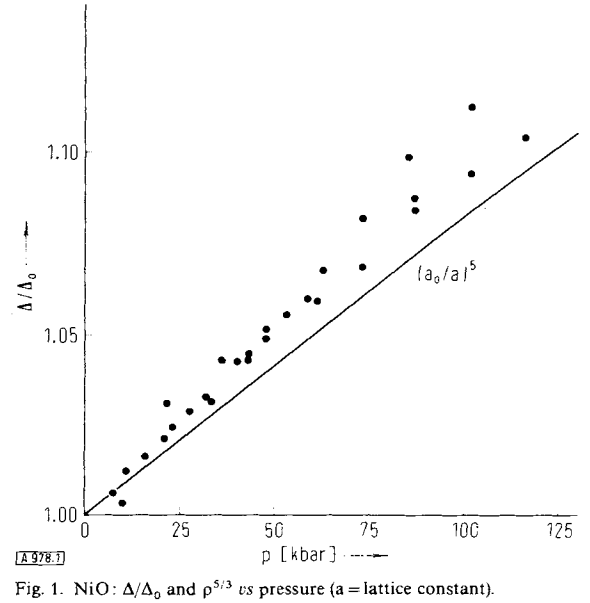


Fig. 1. NiO: Δ/Δ_0 and $\rho^{5/3}$ *vs* pressure (a = lattice constant).

The point charge model is inadequate to calculate Δ even approximately for *any* system, and NiO is far from an ionic crystal so the modest agreement shown may be in large part fortuitous. Measurements on several systems indicate that Δ generally increases somewhat more rapidly with density than the simple model predicts. Figure 2 shows the change in the Racah parameters with pressure for $MnCl_2$ and $MnBr_2$. The decrease shown is typical of most complexes. It is associated with a spreading of the 3d orbitals with pressure and increased shielding of 3d electrons from one another by ligand electrons. The spreading of the 3d orbitals is also reflected in the generally observed decrease of the isomer shift of Fe(II) and Fe(III) ions with pressure (decreased shielding of 3s electrons by 3d electrons) as observed in Mössbauer resonance studies (see Section 3.1).

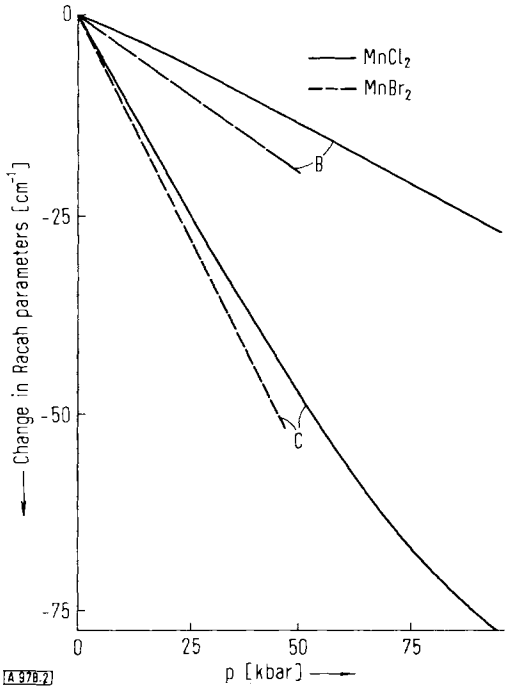


Fig. 2. Change in Racah parameters B and C with pressure for $MnCl_2$ and $MnBr_2$.

2.2. π-π^* Excitations

Aromatic hydrocarbons are characterized by conjugated π orbitals. In the ground state they are nonpolar and not very reactive, especially in solids. There are excited states (π^* states) which have nodes either at or between the carbons. These excited states generally have greater self-complexing ability, are more reactive, and probably involve stronger intermolecular forces than the ground state. The larger the aromatic molecule the smaller the energy of the π-π^* excitation and also the greater the self-complexing ability. These π-π^* excitations decrease in energy by 0.5—1.0 eV per 100 kbars. As discussed later, this implies a higher probability of mixing of π-π^* orbitals and of electron occupation of the π^* orbitals at high pressure.

Heterocyclic aromatic molecules also exhibit π-π^* excitations with very similar characteristics. In Figure 3 we illustrate the shift of a π-π^* excitation in 1,10-phenanthroline. Both the large red shift (to lower energy) and the broadening are typical. These heterocyclic molecules are frequently involved

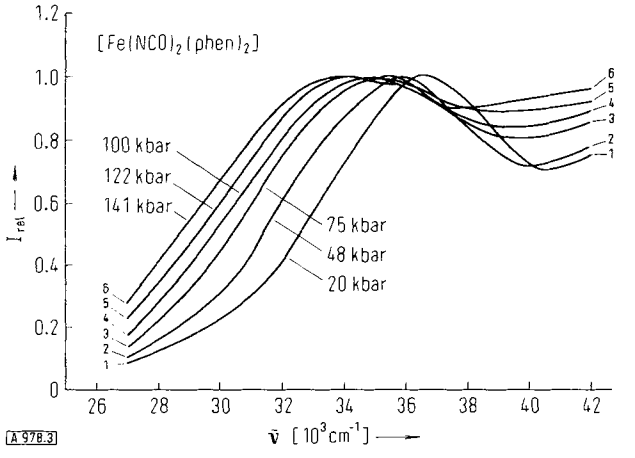


Fig. 3. 1,10-Phenanthroline: π-π^* excitation *vs* pressure.

as ligands in some of the more interesting transition metal complexes.

2.3. Electron Donor-Acceptor Excitations

A wide variety of complexes exhibit relatively intense, broad optical absorption peaks which correspond to electron transfer between two entities of the complex. Molecular electron-donor acceptor complexes have been widely studied[15, 16]. The excitations tend to shift strongly to lower energy with increasing pressure[9, 11]. Similar excitations (ligand to metal or metal to ligand) are frequently observed in transition metal complexes. The halide complexes of the heavy metals (*e.g.* K_2OsBr_6) exhibit a pair of peaks at 16—17 kK and 21—22 kK which *Jørgenson*[17] has assigned to ligand to metal (π-T_{2g}) electron transfer split by spin orbit coupling. As is shown in Figure 4, the center of the peak system shifts to lower energy by some 2.5 kK at 120 kbars, while the spin-orbit splitting increases by $\sim$3.0 kK. A red shift of this magnitude is typical for this type of excitation. Tetrahedral cobalt complexes also exhibit increased spin-orbit splitting at high pressure[10, 11].

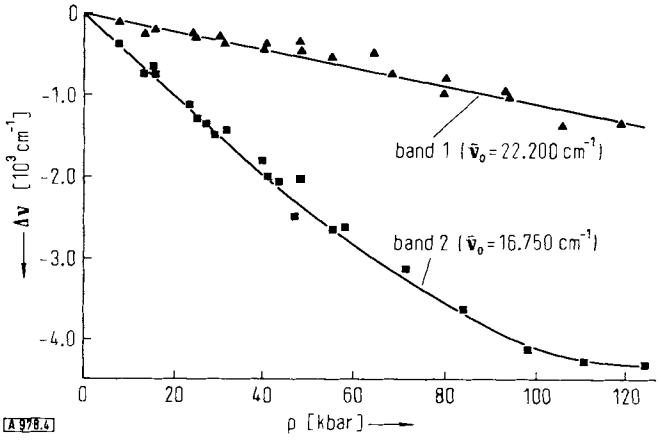


Fig. 4. Location of charge transfer peaks *vs* pressure (K_2OsBr_6).

3. Electronic Transitions

As indicated earlier, the relative shifts in energy levels discussed above can lead to a new ground state for a system, or a ground state whose properties are greatly modified by configuration interaction. Let us first discuss some general characteristics of these electronic transitions, which may occur discontinuously at some definite pressure or over a range of pressures. They may be easily reversible, or may reverse with considerable hysteresis, or may result in a new stable compound. These characteristics are discussed in a detailed study[9, 18] of which we can give only the barest essence here. The various transitions may to a greater or lesser degree be cooperative phenomena. When a site transforms there may be an electrical polarization and/or mechanical strain introduced, which may act either to inhibit or to accelerate the transformation of neighboring sites. The continuous or discontinuous nature of the transformation depends on the sign of the interaction and its magnitude relative to the thermal energy (kT). Hysteresis implies the locking-in of a transformation by interaction among transformed sites.

These transitions involve the thermal transfer of an electron from one type of orbital to another or from one mixture of orbitals to another. Typically, however, we employ optical absorption to measure the shifts in relative energy of the orbitals which ultimately lead to the transition. The energies involved in optical and thermal transfers between the same electronic states differ for a number of reasons. Some of these are illustrated in Figure 5, which is a schematic configuration coordinate diagram. The horizontal axis represents some relative nuclear displacement of the system, while the vertical axis measures energy.

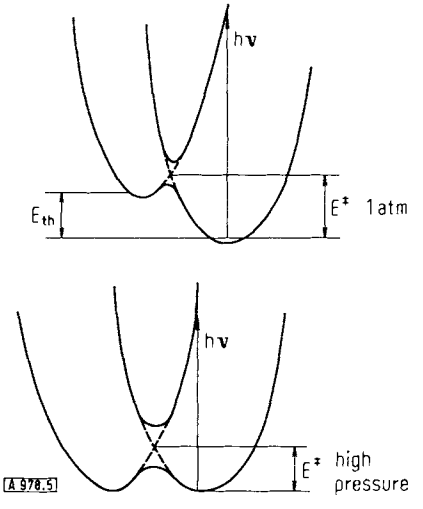


Fig. 5. Schematic configuration coordinate diagram.

Optical processes are represented vertically on such a diagram because they are rapid compared with nuclear displacements (the Franck-Condon principle). Thermal processes are sufficiently slow so that they can occur on a path of minimum energy requirement. This is a major difference, but there are others which can be of comparable magnitude. Configurational interaction, which involves mixing of electronic configurations by partial violation of the Born-Oppenheimer conditions through spin-orbit or other couplings is also illustrated in Figure 5. In solids of the complexity of most of those discussed here there is almost always a vibration suitable enough to mix configurations of any symmetry. A third factor, not illustrated here, is that of selection rules. Optical processes are subject to parity and spin selection rules, while in the time scale typical of thermal processes all selection rules are relaxed.

Finally, Figure 5 is greatly oversimplified in that only one configuration coordinate is illustrated. Actually, the total number of such coordinates equals the number of normal modes of the system. For a thermal process, the pressure selects the volume as its conjugate coordinate, but optical processes may involve other coordinates.

In view of these complications, to what degree can the observed optical shifts be related to the thermal transformations? An analysis has been presented[9, 19] which relates the location of the optical peak (ν_{max}), its half-width ($\delta E_{1/2}$), and the force constants of the ground and excited state potential wells (ω and ω') to the thermal energy (E_{th}). At 25 °C, if the energies are in eV, one obtains:

$$E_{th} = h\nu_{max} - 3.6(\delta E_{1/2})^2 \left(\frac{\omega}{\omega'}\right)^2 \quad (1)$$

This result is based primarily on the Franck-Condon argument. It can be extended to include multiple configuration coordinates, but it is difficult to generalize the magnitude of the effect of configurational interaction. The analysis is approximate and the data to test it are crude; nevertheless, we shall see that useful results are obtained.

It is our purpose here to discuss primarily electronic transitions in transition metal complexes. It is, however, appropriate to outline briefly the other types of electronic transitions which have been observed to place the above in their proper context.

Over 20 years ago *Bridgman*[20] discovered a cusp in electrical resistance and a volume discontinuity in cesium. *Sternheimer*[21] showed that these are associated with a change from s to d character of the conduction band (*i.e.* a 6s→5d transition). About a decade ago a second maximum in the resistance of cesium was observed near 135 kbars. Recent work indicates that hybridization of the empty 4f and atomic 5p orbitals into the conduction band are both involved. Transitions which probably have a similar basis are observed in rubidium at 145 and 300 kbars. A transition in cerium metal near seven kilobars involves promotion of a 4f electron into the 5d shell, or into the conduction band. Resistance anomalies in other rare earth metals at higher pressures may be associated also with 4f→5d transitions. This is consistent with the shift to lower energies of the 4f→5d excitation in divalent rare earth salts which we mentioned earlier. Alkaline earth metals like calcium and strontium exhibit metal to semimetal (or semiconductor) transitions because of changes in the band structure at high pressure.

A variety of insulator-metal transitions have been observed. In molecular crystals like iodine or pentacene the energy gap decreases continuously with pressure, and metallic conductivity appears, with no apparent discontinuity in resistance or structure. Silicon, germanium, and related compounds undergo a first order change in structure which transforms them to metals like tin. Some semiconducting oxides undergo a discontinuous transition without structure change to a metallic state. The work of *McWhan et al.*[22-24] on these compounds has been especially enlightning. In particular these authors have demonstrated the parallelism between change of chemical composition and increase of pressure. *Jayaraman*[25, 26] has shown that samarium chalcogenides transform from semiconductor to metal by promotion of an electron from the 4f orbitals to the conduction band.

Transitions with chemical consequences have been observed in certain aromatic hydrocarbons and their electron donor-acceptor complexes. We have indicated earlier that the π-π^* excitations of these hydrocarbons as well as the D-A excitations of the complexes decrease rapidly in energy with increasing pressure. If the excited state at one atmosphere is not too high in energy, it may be occupied at high pressure with consequent changes in intermolecular interactions including reactivity. It has been observed that pentacene forms a new type of polymer at high pressure[9, 27]. The complexes of perylene ($C_{20}H_{12}$) and pyrene ($C_{16}H_{10}$) with iodine also react[9, 28]. In this case, the iodine does not enter into the product although its presence is necessary to bring the hydrocarbon into a reactive configuration. The product structures have been rather completely elucidated. Perylene forms a new type of layered dimer, while pyrene forms a similar tetramer. These types of reactive electronic transitions may have important implications for solid state organic chemistry.

3.1. Transition Metal Complexes

With this background, we now consider changes of spin state and oxidation state of transition metal complexes. Most of our observations concern complexes of iron. Iron is of interest not only in chemistry and physics but also in biology and geophysics. Further, in addition to optical absorption, we have available Mössbauer resonance spectroscopy to sharpen our identification of the states involved.

We offer only a very brief outline of the principles of Mössbauer resonance here. Under certain circumstances, the energy of a gamma ray emitted by ^{57}Fe in the solid state is a measure of the separation of nuclear energy levels. This separation is perturbed by electronic wave functions. From the measured perturbations information can be inferred about the electronic structure—very much as in the employment of nuclear magnetic resonance. For this study there are two useful types of pertubation. Electronic wave functions which overlap the nucleus (s electrons) affect the energy difference between the ground and excited state (the isomer shift). From our viewpoint, changes in the isomer shift reflect changes in shielding of 3s electrons by 3d electrons. This depends on the number of 3d electrons (oxidation state) and the radial extent and shape of the 3d orbitals (covalency). An electric field gradient at the iron nucleus partially removes the degeneracy of the excited state and gives two peaks in the spectrum instead of one. The electric field gradient may arise from the arrangement of the ligands (a long range, small effect) or from the partially filled 3d shell (a short range, large effect). Because of these perturbations ^{57}Fe in one chemical state is not in resonance with ^{57}Fe in a different state. By moving a radioactive source with respect to an absorber we utilize the Doppler velocity to bring about resonance, and express the perturbation energies in terms of this resonant velocity.

We are concerned here primarily with transformations involving three states; high-spin ferrous, high-spin ferric, and low-spin ferrous. Figure 6 exhibits typical spectra for these states. The high-spin ferrous ion exhibits a large positive isomer shift (IS) (low electron density) because of the six 3d electrons shielding the 3s electrons, and a large quadrupole splitting (QS) because the field of the 3d electrons is not spherically symmetric. The high-spin ferric ions with five 3d electrons

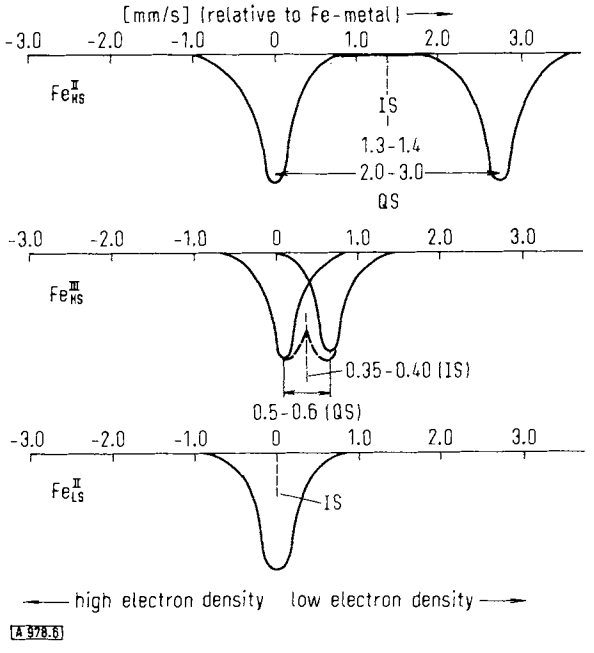


Fig. 6. Characteristic Mössbauer spectra.

has a smaller isomer shift, and, since the field of the 3d shell is spherical, only a small quadrupole splitting. The low-spin ferrous ion has a spherical electric field and thus a small quadrupole splitting. The low value of the isomer shift reflects the delocalization of the 3d electrons by "back donation" as discussed in Section 2.1, and the resultant high electron density at the nucleus. Our discussion will be largely limited to three transitions: 1. Fe^{II}_{HS} (high spin) → Fe^{II}_{LS} (low spin); 2. Fe^{II}_{LS} → Fe^{II}_{HS}; 3. Fe^{III}_{HS} → Fe^{II}_{HS}.

3.1.1. Spin Changes

We consider first the high-spin to low-spin transition. Since, as shown in Section 2.1, the ligand field increases with pressure, one might expect that at some pressure, Δ could become larger than the spin pairing energy. One example is Fe(II) as a dilute substitutional impurity in MnS_2. In the isomorphous FeS_2 (pyrites), iron is low spin at all pressures. Since the lattice parameter of MnS_2 is distinctly larger than that of FeS_2 it is not surprising that iron in MnS_2 is high spin. One can think of the Fe(II) as being under a large negative pressure in MnS_2 relative to its situation in FeS_2. Figure 7 shows the Mössbauer spectra as a function of pressure. At low pressure (up to 40 kbars) one sees only the Fe^{II}_{HS} spectra. At 65 kbars the iron is over 50% converted to low spin. At 138 kbars the conversion is complete. The process is reversible with some hysteresis. This is, then, a transition from a paramagnetic to a diamagnetic ground state.

Let us now consider the transition from Fe^{II}_{LS} to Fe^{II}_{HS} with increasing pressure. We first look at the evidence for this somewhat surprising event. We consider complexes of iron with 1,10-phenanthroline. In tris complexes each of three phenanthrolines complexes through two nitrogens so that the Fe(II) is in an approximately octahedral field of six nitrogens. Because of back donation (see Section 2.1) to the ligands Δ is 2.0—2.5 eV and the iron is low spin. Figure 8 shows Mössbauer spectra as a function of pressure. At low pressure one observes only low spin iron. Above ~40 kbars a measurable amount of Fe^{II}_{HS} appears; and at 140 kbars there is about 30% conversion. Complexes involving substituted phenanthrolines may exhibit up to 60% conversion. The process is reversible, with hysteresis.

Complexes also form with two molecules of phenanthroline and two other ligands. These bis complexes are usually high spin at one atmosphere. At a modest pressure they convert partially or even completely to low spin, but above about 40—50 kbars the amount of high spin again increases[9, 29, 30].

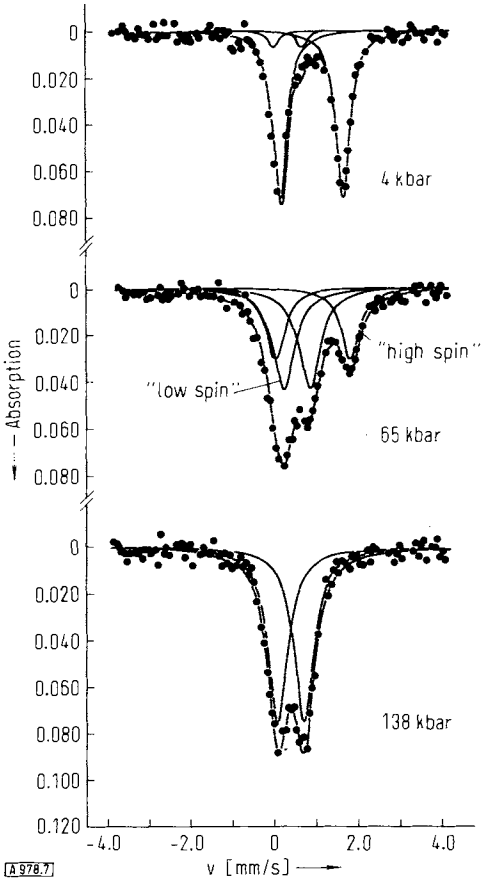


Fig. 7. Mössbauer spectra of Fe^{II} in MnS_2 at 4 kbar, 65 kbar, and 138 kbar.

The LS→HS transition seems paradoxical at first on both thermodynamic and electronic grounds. One must remember that it is the volume of the system *as a whole* which must decrease with increasing conversion at constant *T* and *p*. This volume decrease may involve changes in intermolecular forces as well as bond lengths. It is not, of course, necessary that any particular bond must shorten.

The back donation which provides the large ligand field depends on the availability of the ligand π* orbitals. As already shown (Fig. 3), the π-π* energy difference decreases rapidly with pressure. If there is significant mixing of the π and π* orbitals they will become less available for back donation from the iron. In Table 1 a calculation for phenanthroline is given using Eq. (1). At one atmosphere the π orbital is stable by about 1.35 eV. Above 50 kbars the energy difference is such that there could be considerable thermal π-π* transfer and hybridization inhibiting back donation. The calculation is very crude, but it illustrates that the hypothesis is feasible. This could be called an induced electronic transition, since a transformation on the ligand changes the bonding to the iron and thus its spin state.

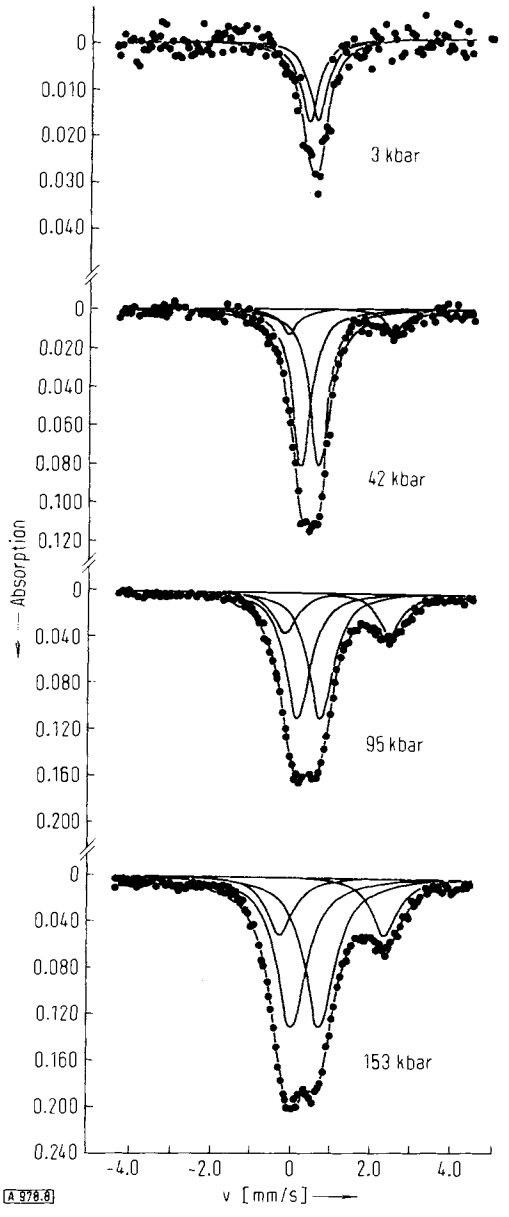


Fig. 8. Mössbauer spectra of Fe^{II} in $Fe(phen)_3Cl_2 \cdot 7H_2O$ at various pressures.

Table 1. Comparison of the energies associated with thermal and optical excitation: π-π^* transition in 1,10-phenanthroline.

p (kbar)	$h\nu_{max}$ [eV]	$\delta E_{1/2}$ [eV]	E_{th} [eV]
0	4.6	0.95	+1.35
50	4.45	1.05	+0.45
100	4.30	1.14	−0.40
150	4.20	1.20	−0.98

One would expect that, at any pressure, the amount of low spin present for a series of related compounds would depend on the size of the ligand field. Δ is difficult to measure directly for these complexes, but it has been shown[31] that there is a good correlation between the Fe^{II}_{LS} isomer shift and Δ; the smaller the isomer shift (*i. e.* the larger the back donation) the larger is Δ. Figure 9 shows the relative amounts of Fe^{II}_{HS} and Fe^{II}_{LS} at 100 kbars for a series of substituted phenanthrolines. It can be seen that the correlation with the isomer shift of Fe^{II}_{LS} is, indeed, very good.

An increase in spin multiplicity with pressure has also been observed in other iron compounds. The ferrocyanides are low spin compounds with relatively large ligand fields. At room temperature they remain low spin to 200 kbars, at least. However, at 100 °C and 150 kbars $Cu_2Fe(CN)_6$ exhibits

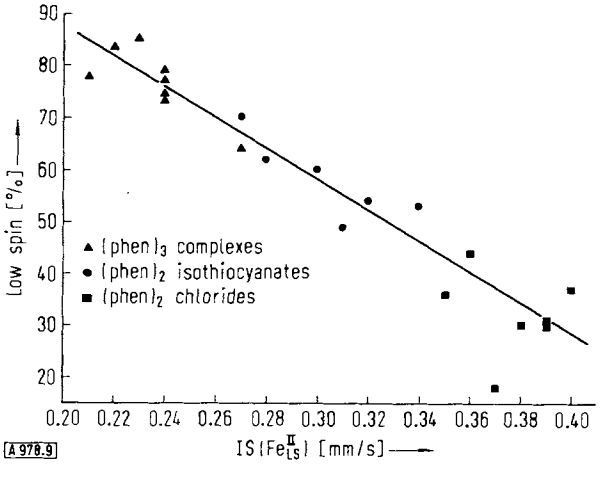


Fig. 9. Percent low spin Fe^{II} *vs* Fe^{II}_{LS} isomer shift in phenanthroline complexes.

65% high spin ferrous ion and $Ni_2Fe(CN)_6 \sim 18$—20%. $Zn_2Fe(CN)_6$, which is isomorphous, shows no conversion. Neither do the sodium nor potassium salts with slightly different structure. At 150 °C and 150 kbars the zinc salt shows ~25% conversion and the sodium and potassium salts only small traces thereof. Apparently cation electrons also interact with the ligand orbitals in these compounds.

One also observes an increase in spin state with pressure in some substituted ferrous phthalocyanines[9, 32]. This planar molecule involves four pyrrole rings bridged by nitrogens with the iron in a site of D_{4h} symmetry. The iron is in an intermediate spin state. When pyridines or picolines are coordinated axially to the iron a low spin Fe(II) (S=O) state results, primarily because of back donation to the nitrogens on the axial ligands. At high pressure a partial conversion of low spin to intermediate spin iron is observed as the back donation is reduced.

3.1.2. Reduction of Fe(III) and Cu(II)

The third electronic transition of interest here is the reduction of Fe^{III}_{HS} to Fe^{II}_{HS} with pressure. Recent studies on Cu(II) are also discussed briefly. Once again Mössbauer spectra are presented as primary evidence. In Figure 10 we show an Fe(III) spectrum at low pressure, the continuing increase in the amount of Fe^{II}_{HS} with pressure, and the reversibility (with hysteresis) upon release of pressure. The reduction takes place by transfer of a ligand electron (probably from a nonbonding orbital) to the metal 3d orbital. The electron and the hole on the ligand probably remain closely associated. There should be a definite relationship between the amount of reduction (*i. e.* the fraction of ferric sites still present) and the area under a ligand-metal charge transfer peak in the optical spectrum. Figure 11 exhibits such a relationship for two hydroxamate-iron complexes (AHA = acetohydroxamic acid, SHA = salicylhydroxamic acid) and a protein (FA = ferrichrome A) which complexes to Fe(III) through three hydroxamate groups. The solid line shows the conversion obtained from Mössbauer measurements while the points represent relative area under the optical absorption peak. The agreement is good.

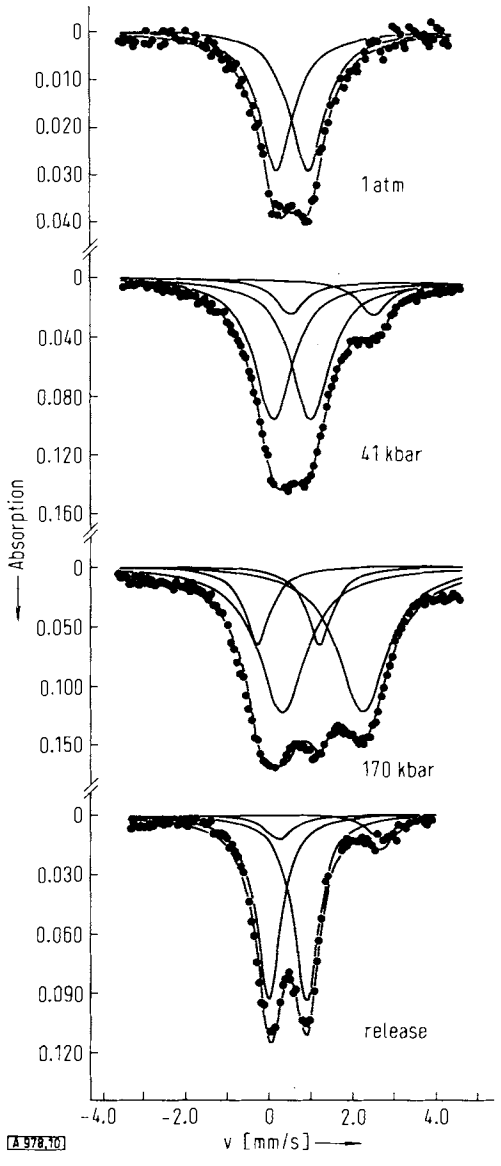


Fig. 10. Mössbauer spectra of tris(2,4-pentanedionato)iron(III) at various pressures.

One would expect that, for a series of related compounds, the conversion would correlate with the electron donor abilities of the ligands. One such study involves the chelates of β-diketones shown in Table 2[9, 33]. At one atmosphere one can measure relative donor character of the ligands by such parameters as the acid dissociation constant, the Hammett σ, the appearance potential from mass spectroscopy, or the half wave potential from polarography. These measurements cannot be obtained on the solid under pressure. However, they correlate well with the ferric isomer shift; a lower isomer shift corresponds to better donor ability. With increasing pressure, the ligand nonbonding orbitals approach the metal 3d orbitals in energy, so the reduction, in general, increases with pressure. This tendency will be augmented in those systems where the isomer shift decreases (relative electron donor ability increases) with pressure, and diminished where the isomer shift increases (relative donor ability decreases). Figure 12 shows the change of conversion between 60 and 160 kbars for the series of compounds of Table 2, plotted against the change of isomer shift in this pressure range. The expected relationship applies very well.

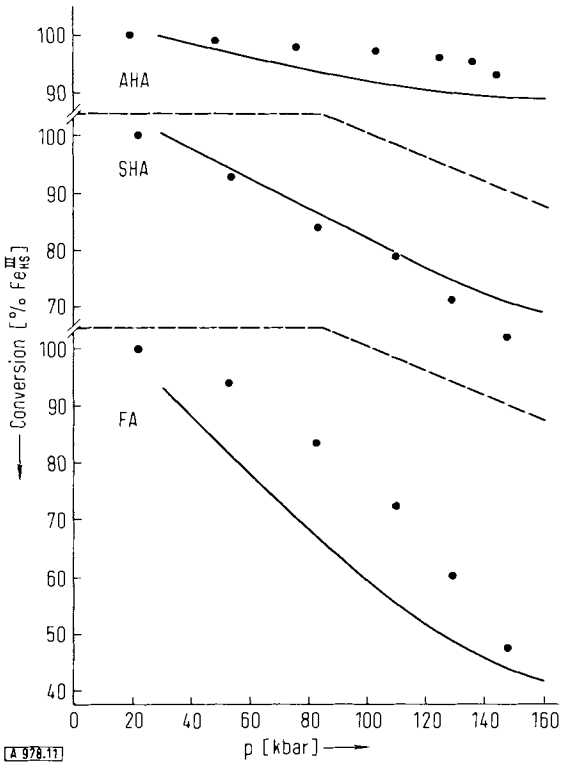
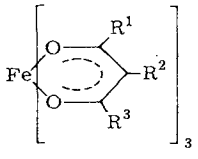


Fig. 11. Comparison of conversion of Fe^{III} to Fe^{II}—from optical (•) and Mössbauer data (—).

Table 2. Tris(β-diketonato)iron(III) complexes.



Ligand	R^1	R^2	R^3
(1)	CH_3	H	CH_3
(2)	C_6H_5	H	C_6H_5
(3)	$C(CH_3)_3$	H	$C(CH_3)_3$
(4)	C_6H_5	H	CH_3
(5)	CF_3	H	CH_3
(6)	CF_3	H	2-Furyl
(7)	CF_3	H	2-Thienyl
(8)	CF_3	H	C_6H_5
(9)	CH_3	CH_3	CH_3
(10)	CH_3	C_6H_5	CH_3
(11)	CH_3	NO_2	CH_3
(12)	CH_3	C_2H_5	CH_3

We can also use Eq. (1) to relate the location and half-width of the charge transfer peak to the reduction of Fe(III). In Table 3 there are shown, for three ferric hydroxamates and the related protein ferrichrome A, the pressure at which 10% reduction occurs, the location and half-width of the charge transfer peak, and the resultant value of E_{th} (assuming $\omega = \omega'$). It can be seen, as one would expect, that within the accuracy of the data and of the analysis $E_{th} \approx 0$.

A recent study[34] on complexes of Cu(II) with organic ligands shows that reduction occurs for these compounds also at high pressure. Cu(II) has nine 3d electrons and Cu(I) has ten. Because of the filled 3d shell, Cu(I) has no d-d excitations. As illustrated in Fig. 13 for $Cu(dtc)_2$ (dtc = diethyldithiocarbamate) the conversion is demonstrated by a decrease in integrated intensity of the Cu(II)-ligand charge transfer peak (b)

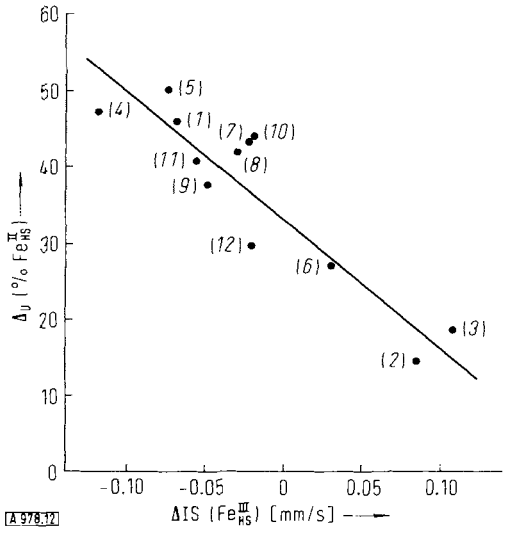


Fig. 12. Change in conversion of Fe^{III} to Fe^{II} *vs* change in isomeric shift between 60—160 kbar.

Table 3. Optical and thermal excitation: Ligand-metal charge transfer in ferric hydroxamates and ferrichrome A (10% reduction of Fe(III).

Ligand	p [kbar]	$h\nu_{max}$ [eV]	$\delta E_{1/2}$ [eV]	E_{th} [eV]
AHA	125	2.80	0.90	0.11
BHA	105	2.70	0.875	−0.06
SHA	70	2.54	0.84	−0.02
FA	37	2.65	0.835	+0.11

and growth of a new peak (c) at lower energy—in a region typical for cuprous charge transfer peaks. Furthermore, the d-d excitation [peak (a)] near 16 kK also decreases in intensity as one would expect.

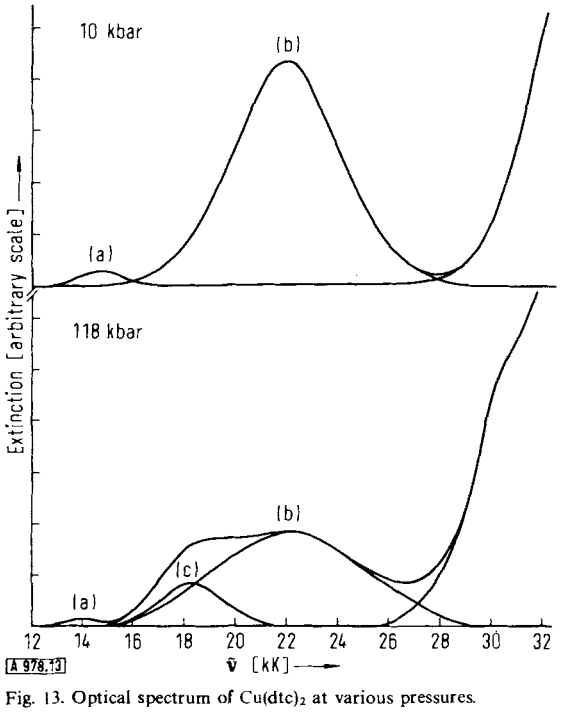


Fig. 13. Optical spectrum of $Cu(dtc)_2$ at various pressures.

The ferric porphyrins have been widely studied as prototypes for hemoglobin, although the applicability is limited by the fact that iron in hemoglobin is apparently in the ferrous state. Porphyrin is a planar molecule with four pyrrole rings connected by methine groups. There are various substituents on the periphery of the pyrroles. In hemin and hematin there is respectively, one Cl^- or one OH^- coordinated axially to the iron which is some 0.5 Å out of the plane of the ring and is high spin. The high spin state would be very improbable with the iron in the plane. In imidazole protoheme two imidazoles are coordinated axially to the iron which is in the plane of the ring and is low spin. Of course, it is something of an oversimplification to speak of definite spin states and oxidation states for iron where the bonding is so complex.

With pressure the ferric ion reduces in all three compounds[9]. At relatively high pressure the ferrous ion produced appears to be in an intermediate spin state in all three cases. For the imidazole protoheme the increase in spin multiplicity is caused by decreased back donation to the imidazoles. For the hemin and hematin the decrease in spin state is apparently associated with the effect of pressure in forcing the iron back into the molecular plane. The large increase in the ferric quadrupole splitting which is observed is consistent with this interpretation.

These reductions illustrate an electronic transition resulting from the shift of energy levels of one member of a complex (the ligand) with respect to those of the other member (the metal).

4. Summary

We have shown that pressure has a very significant effect on the relative energy of electronic orbitals. In a wide variety of circumstances the relative change in energy is sufficient to establish a new, or a greatly modified ground state. These electronic transitions occur in a wide variety of materials; here we have emphasized changes in the coordination chemistry of transition metal ions. It is hoped that this brief outline will amply demonstrate the power of pressure as a tool for investigating electronic structure.

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[1] *P. W. Bridgman:* Physics of High Pressure. G. Bell and Sons, London 1949.

[2] *E. U. Franck*, Ber. Bunsenges. Phys. Chem. *70*, 944 (1966).

[3] *J. Jones*, Advan. Magn. Resonance *6*, 73 (1973).

[4] *O. E. Weigang, Jr.* and *W. W. Robertson*, High Pressure Phys. Chem. *1*, 177 (1963).

[5] *K. E. Weale:* Chemical Reactions at High Pressures. Spon. Ltd., London 1972.

[6] *C. A. Eckert*, Annu. Rev. Phys. Chem. *23*, 239 (1972).

[7] *R. J. Wentorf, Jr.:* Modern Very High Pressure Techniques. Butterworths, London 1962.

[8] *C. C. Bradley:* High Pressure Methods in Solid State Research. Butterworths, London 1969.

[9] *H. G. Drickamer* and *C. W. Frank:* Electronic Transitions and the High Pressure Chemistry and Physics of Solids. Chapman and Hall, London 1973.

[10] *H. G. Drickamer* in *W. Paul* and *D. Warschauer:* Solids Under Pressure. McGraw-Hill, New York 1963.

[11] *H. G. Drickamer*, Solid State Phys. *17*, 1 (1965).

[12] *H. G. Drickamer* and *J. C. Zahner*, Advan. Chem. Phys. *4*, 161 (1962).

[13] *H. G. Drickamer* and *C. W. Frank*, Annu. Rev. Phys. Chem. *23*, *39* (1972).

[14] *P. J. Wang* and *H. G. Drickamer*, J. Chem. Phys. *58*, 4444 (1973).

[15] *R. S. Mulliken* and *W. B. Person:* Molecular Complexes. Wiley, New York 1969.

[16] *R. Foster*: Organic Charge Transfer Complexes. Academic Press, London 1969.

[17] *C. K. Jørgensen*, Mol. Phys. 2, 309 (1959).

[18] *C. P. Slichter* and *H. G. Drickamer*, J. Chem. Phys. 56, 2142 (1972).

[19] *H. G. Drickamer*, *C. W. Frank*, and *C. P. Slichter*, Proc. Nat. Acad. Sci. USA 69, 933 (1972).

[20] *P. W. Bridgman*, Proc. Amer. Acad. Arts Sci. 76, 55 (1948).

[21] *R. Sternheimer*, Phys. Rev. 78, 235 (1950).

[22] *D. B. McWhan*, *T. M. Rice*, and *J. Remeika*, Phys. Rev. Lett. 23, 1384 (1969).

[23] *D. B. McWhan* and *J. Remeika*, Phys. Rev. *B* 2, 3734 (1970).

[24] *A. Jayaraman*, *D. B. McWhan*, *J. Remeika*, and *P. D. Dernier*, Phys. Rev. *B* 2, 3751 (1970).

[25] *A. Jayaraman*, *V. Narayanamurti*, *E. Bucher*, and *R. G. Maines*, Phys. Rev. Lett. 25, 368, 1430 (1970).

[26] *A. Chatterjee*, *A. K. Singh*, and *A. Jayaraman*, Phys. Rev. *B* 6, 2285 (1972).

[27] *V. C. Bastron* and *H. G. Drickamer*, J. Solid State Chem. 3, 550 (1971).

[28] *M. I. Kuhlman* and *H. G. Drickamer*, J. Amer. Chem. Soc. 94, 8325 (1972).

[29] *D. C. Fisher* and *H. G. Drickamer*, J. Chem. Phys. 54, 4825 (1971).

[30] *C. B. Bargeron* and *H. G. Drickamer*, J. Chem. Phys. 55, 3471 (1971).

[31] *N. E. Erickson* in *R. F. Gould*: Mössbauer Effect and Its Application in Chemistry. Amer. Chem. Soc., Washington 1967.

[32] *D. C. Grenoble* and *H. G. Drickamer*, J. Chem. Phys. 55, 1624 (1971).

[33] *C. W. Frank* and *H. G. Drickamer*, J. Chem. Phys. 56, 3551 (1972).

[34] *P. J. Wang* and *H. G. Drickamer*, J. Chem. Phys. 59, 713 (1973).

The Variety of Thermal Pericyclic Reactions

By James B. Hendrickson[*]

The six-electron thermal pericyclic reactions are examined systematically as to the number and kind which are possible by varying both the σ shell and the combinations of different atoms in all orientations, on both a six-atom and a five-atom framework. A simple unifying nomenclature is offered for these reactions, which number in the thousands. Further, in order to comprehend this very large number of possible reactions, they are also organized systematically in terms of their value for basic synthesis operations: construction, elimination, refunctionalization, *etc.* The methodology is aimed at providing a basis of selection for the invention of useful new reactions. A discussion of reaction energetics leads also to an analysis of molecular features which can facilitate reaction.

1. Introduction

The common thermal pericyclic reactions[1] are characterized by a cyclic transition state of three pairs of electrons, stabilized by an optimal overlap of all involved orbitals and by the delocalization of six electrons in a cycle. This resonance stabilization of six electrons in a cyclic transition state was early recognized by *Evans*[2], and *Dewar*[3a] has recently discussed pericyclic reactions in terms of the analogy with aromatic systems. Any cycle of $(4n+2)$ delocalized electrons[3b] is the basis for a stabilized aromatic molecule as well as a set of pericyclic reactions, derived formally as shown below by removal of various of the σ bonds in the underlying molecular frame.

The reactions are equilibria and a rough calculation of bond energies usually identifies the more stable molecular species and preferred direction of reaction. As the generalized reaction is nominally unaffected by changes in the involved atoms or by other molecular species present (*e.g.*, reagents, solvents) it is capable of considerable variety as well as synthetic utility. In the latter connection it is often an excellent means of generating carbon-carbon bonds or hindered, sensitive, or otherwise difficultly accessible molecular groups, generally with a high order of stereospecificity. The purpose of this article is to examine the number and form of all the theoretically possible variants of the reaction obtainable by varying the σ-bond shell linking the involved atoms as well as by varying the involved atoms themselves.

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2. The Six-Center Model

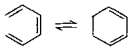
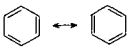
The problem of molecular permutations may be approached by writing the three shifting electron pairs as alternating bonds around a six-atom cycle and then generating all combinations of 0 to 6 immobile σ bonds (B) linking these atoms. These immobile σ bonds constitute the "shell" or backbone of the reacting species. There are thirteen possible shells, shown in Table 1 with and without the three shifting electron pairs. The shells are defined specifically as σ bonds; in some cases extra π bonds occur, as in Diels-Alder addition to acetylenic dienophiles, but these are involved neither in the skeletal shell nor in the shifting electron set and so are not separated in the definition. The reacting pairs of molecules are all oriented in Table 1 with the more stable form on the right and its energy preference as calculated from bond energies for the all-carbon (C_6) example; with other combinations of atoms, of course, the equilibrium preference may be reversed. In six of the thirteen cases the two forms are identical in the parent example shown.

The variety of shells as well as the variety of atom combinations parallels the variety of polysubstituted benzenes in orientation and the letter notation used here is the same as that recently introduced for polysubstituted benzenes[4]. All the shells except $B=3_L$ possess symmetry: two kinds of two-fold (plane/axis through opposite atoms in $B=2_O$ and 4_U or opposite bonds in $B=1$, 2_M, 3_V, 4_T and 5); four-fold in $B=2_P$ and 4_X; and

Table 1. Combinations of six-center thermal pericyclic reactions.

Shell	Symmetry	Reaction [a, d]	Atoms [b]	C_5Z	C_4Z_2 [c] O	M	P	C_3Z_3 [c] V	L	Δ	Σ
B=0		(111111) 0	N	1	1	1	1	1	1	1	7
			O	1	1	1	1	1	1	1	7
			NO		2	1	1	—	—	—	4
			N_2O					3	6	1	10
			NO_2					3	6	1	10
			Σ	2	4	3	3	8	14	4	38
B=1		(112211) 25	N	3	4	3	2	3	6	1	22
			O	3	4	3	2	3	6	1	22
			NO		6	6	3	—	—	—	15
			N_2O					9	18	3	30
			NO_2					9	18	3	30
			Σ	6	14	12	7	24	48	8	119
B=2	O	(321112) 0	N	4	3	4	2	4	6	2	25
			O	3	2	3	1	3	3	1	16
			NO		5	5	3	—	—	—	13
			N_2O					8	15	3	26
			NO_2					7	12	3	22
			Σ	7	10	12	6	22	36	9	102
	M	(221122) 50	N	3	4	3	2	3	6	1	22
			O	3	4	3	2	3	6	1	22
			NO		6	6	3	—	—	—	15
			N_2O					9	18	3	30
			NO_2					9	18	3	30
			Σ	6	14	12	7	24	48	8	119
	P	(122122) 0	N	2	2	2	2	2	3	1	14
			O	2	2	2	2	2	3	1	14
			NO		3	3	2	—	—	—	8
			N_2O					4	9	2	15
			NO_2					4	9	2	15
			Σ	4	7	7	6	12	24	6	66
B=3	Δ	(222222) 75	N	1	1	1	1	1	1	1	7
			O	1	1	1	1	1	1	1	7
			NO		2	1	1	—	—	—	4
			N_2O					3	6	1	10
			NO_2					3	6	1	10
			Σ	2	4	3	3	8	14	4	38
	L	(212322) 25	N	6	6	6	3	6	12	2	41
			O	5	4	4	2	3	6	1	25
			NO		10	10	5	—	—	—	25
			N_2O					15	30	5	50
			NO_2					12	24	4	40
			Σ	11	20	20	10	36	72	12	181
	V	(321123) 25	N	3	4	3	2	3	6	1	22
			O	2	2	1	1	1	1	0	8
			NO		4	4	2	—	—	—	10
			N_2O					6	12	2	20
			NO_2					4	7	1	12
			Σ	5	10	8	5	14	26	4	72
B=4	X	(322322) 0	N	2	2	2	2	2	3	1	14
			O	1	1	1	1	0	1	0	5
			NO		2	2	1	—	—	—	5
			N_2O					3	6	1	10
			NO_2					2	4	1	7
			Σ	3	5	5	4	7	14	3	41
	T	(322323) 50	N	3	4	3	2	3	6	1	22
			O	2	2	1	1	1	1	0	8
			NO		4	4	2	—	—	—	10
			N_2O					6	12	2	20
			NO_2					4	7	1	12
			Σ	5	10	8	5	14	26	4	72
	U	(123332) 0	N	4	3	4	2	4	6	2	25
			O	2	1	1	0	1	0	0	5
			NO		3	3	2	—	—	—	8
			N_2O					5	9	2	16
			NO_2					3	3	1	7
			Σ	6	7	8	4	13	18	5	61

Table 1. (continued)

Shell	Symmetry	Reaction [a,d]	Atoms [b]	C_5Z	C_4Z_2 [c] O	M	P	C_3Z_3 [c] V	L	Δ	Σ
B=5		 (233332) 25	N	3	4	3	2	3	6	1	22
			O	1	1	0	0	0	0	0	2
			NO		2	2	1	—	—	—	5
			N_2O					3	6	1	10
			NO_2					1	1	0	2
			Σ	4	7	5	3	7	13	2	41
B=6		 (333333) 0	N	1	1	1	1	1	1	1	7
			O	0	0	0	0	0	0	0	0
			NO		0	0	0	—	—	—	0
			N_2O					0	0	0	0
			NO_2					0	0	0	0
			Σ	1	1	1	1	1	1	1	7
			ΣΣ	62	113	104	64	190	354	70	957
					281			614			

[a] Circled atoms transferred *via* σ-bonds; numbers under structures are calculated equilibrium preferences (kcal/mol) for the C_6 cases.
[b] N, O are generalized for v=3 and v=2 atoms or groups, respectively.
[c] Orientations of hetero-atoms (Z) shown.
[d] In parenthesis for each shell are shown the minimum obligatory valencies for each of the six atoms, listed in clockwise order from a symmetry element (*i.e.*, from an atom # 1).

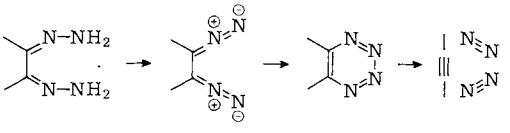
six-fold in B=0, 3_Δ and 6. The numbers of identifiably different positions on the shells are also entered, clockwise from a symmetry element.

The various shells are also characterized by the mode of reaction in each direction, *i.e.*, by the number of reacting molecules or components and by the number of components formed. Thus *cycloadditions* are characterized by the combined reaction of two (or three) components, *fragmentations* and *rearrangements* by the transformation of one molecule into, respectively, two or more components, or simply a rearranged one; the rearrangements are sigmatropic (B=4_X and 4_U) or electrocyclic (B=5). The full-shell case of B=6 is then the parent aromatic case, the valence-bond description of benzene, or, with other atom combinations, of pyridine, pyrimidine, pyrylium salts, *etc.*

	forward	reverse
Cycloaddition	B=0, 1, 2, 3, 4_T	B=0, 1, 2_O, 2_P
Fragmentation	none	2_M, 3, 4_T
Rearrangement	4_X, 4_U, 5	4_X, 4_U, 5

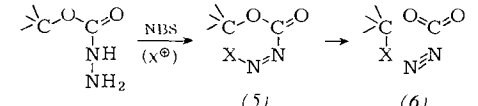
Each atom position in any shell has an obligatory minimum formal valency (v=1, 2, or 3), indicated by the number of bonds incident to each atom in Table 1. The six required minimum valencies for each shell are listed. The maximum valency of v=3 is found for B=6. For instance, the valency list for B=4_T is 322223. In all cases B≤3 (with the exception of B=3_Δ) and also 4_U there are atoms of minimum valency v=1. These are singly σ-bonded atoms which are transferred from one cyclic atom to another. This *σ-transfer* is of special interest in synthetic chemistry for atoms other than hydrogen. A few cases are known with free carbon groups (not elsewhere cyclically bonded to the skeleton) transferred in this fashion[5, 6], all of them sigmatropic rearrangements, but in most cases of this sort[1] it is hydrogen (v=1) which is transferred.

Heteroatoms or groups of v=2 include O, S, SO, SO_2, and N—R, while those of v=3 are primarily N but may also be P or O^+, and any valency can be represented by an appropriate metal atom or ion. The number of combinations created by placing atoms of v=1, 2, or 3 in the various positions in each shell may now be tabulated. These are shown in Table 1, groups of v=3, 2, and 1 being symbolized respectively as N, O, and H. The orientation of heteroatom placement on the six-atom cycle follows again the same pattern of combinations as do the shells and the polysubstituted benzenes[4]. The notation used is C_5Z=monosubstituted shell; C_4Z_2=two heteroatoms: *ortho* (O), meta (M), *para* (P); C_3Z_3=three heteroatoms: V, L, Δ; *etc.* The maximum number of combinations is found in the B=3_L form since it possesses no symmetry. Table 1 lists only the variations in v=3 and 2 sites (N and O), the v=1 (H) site variations being shown in Table 2. The replacement of more than three carbons by heteroatoms has not been tabulated owing to the increase in possible N_nO_m combinations and the low likelihood of there being viable reactions in many cases with four or five (often vicinal) heteroatoms in the cycle[7]. However, some are known reactions. Thus the oxidation of 1,2-bishydrazones to acetylenes[8] may proceed as *(1)*→*(2)*→*(3)*→*(4)*, the final reaction being B=$3_\Delta(C_2N_4)_O$.



(1) *(2)* *(3)* *(4)*

Similarly, the recently discovered pericyclic refunctionalization of alcohols[9], *(5)*→*(6)*, has the form B=$2_M(C_2N_2OX)$, with only two carbons in the cycle. The example also exhibits σ-transfer of both C and H.



NBS = *N*-bromosuccinimide *(5)* *(6)*

Table 2. Combinations of six-center thermal pericyclic reactions involving hydrogen.

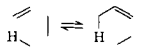
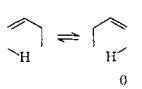
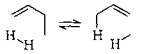
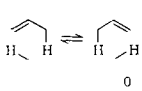
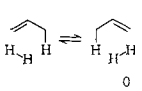
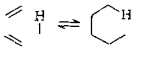
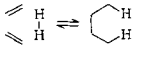
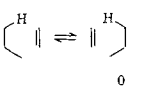
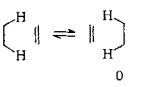
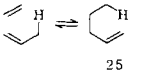
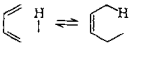
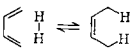
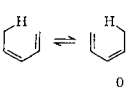
Shell	Symmetry	Reaction [a]	Atoms [b]	Z_1 [c]	Z_2 [c] O	M	P	Z_3 [c] V	L	Δ	Σ
$B=2_O$		 0	N	5	4	3	2	3	6	1	24
			O	4	2	2	1	1	3	1	14
			NO		6	5	3	—	—	—	14
			N_2O					7	14	3	24
			NO_2					5	10	3	18
			Σ	9	12	10	6	16	33	8	94
		 0	N	3	2	3	1	2	3	1	15
			O	2	1	2	1	0	2	0	8
			NO		3	3	2	—	—	—	8
			N_2O					3	8	1	12
			NO_2					2	7	1	10
			Σ	5	6	8	4	7	20	3	53
		 0	N	4	3	2	1	2	2	0	14
			O	3	1	1	1	0	1	0	7
			NO		4	3	2	—	—	—	9
			N_2O					4	5	0	9
			NO_2					2	4	0	6
			Σ	7	8	6	4	8	12	0	45
		 0	N	3	2	2	1	1	1	1	11
			O	2	0	2	0	0	0	1	5
			NO		2	3	1	—	—	—	6
			N_2O					1	2	2	5
			NO_2					1	1	2	4
			Σ	5	4	7	2	3	4	6	31
		 0	N	2	1	1	0	1	0	0	5
			O	1	0	1	0	0	0	0	2
			NO		1	1	0	—	—	—	2
			N_2O					1	0	0	1
			NO_2					1	0	0	1
			Σ	3	2	3	0	3	0	0	11
$B=2_M$		 50	N	5	4	4	2	3	8	1	27
			O	5	4	4	2	3	8	1	27
			NO		8	8	4	—	—	—	20
			N_2O					6	24	3	33
			NO_2					6	24	3	33
			Σ	10	16	16	8	18	64	8	140
		 50	N	2	2	1	1	1	1	0	8
			O	2	2	1	1	1	1	0	8
			NO		3	2	1	—	—	—	6
			N_2O					3	3	0	6
			NO_2					3	3	0	6
			Σ	4	7	4	3	8	8	0	34
$B=2_P$		 0	N	3	2	3	1	2	3	1	15
			O	3	2	3	1	2	3	1	15
			NO		4	4	2	—	—	—	10
			N_2O					5	9	2	16
			NO_2					5	9	2	16
			Σ	6	8	10	4	14	24	6	72
		 0	N	1	1	1	1	0	1	0	5
			O	1	1	1	1	0	1	0	5
			NO		1	1	1	—	—	—	3
			N_2O					0	3	0	3
			NO_2					0	3	0	3
			Σ	2	3	3	3	0	8	0	19
$B=3_L$		 25	N	5	4	4	2	3	6	1	25
			O	4	2	3	1	1	2	1	14
			NO		6	7	3	—	—	—	16
			N_2O					7	14	3	24
			NO_2					5	10	3	18
			Σ	9	12	14	6	16	32	8	97
$B=3_V$		 25	N	5	4	4	2	3	6	1	25
			O	3	1	1	1	0	1	0	7
			NO		4	5	3	—	—	—	12
			N_2O					4	12	2	18
			NO_2					1	7	1	9
			Σ	8	9	10	6	8	26	4	71

Table 2. (continued)

Shell	Symmetry	Reaction [a]	Atoms [b]	Z_1 [c]	Z_2 [c] O	M	P	Z_3 [c] V	L	Δ	Σ
		 25	N	2	2	1	1	1	1	0	8
			O	1	0	0	1	0	0	0	2
			NO		1	1	1	—	—	—	3
			N_2O					1	2	0	3
			NO_2					0	1	0	1
			Σ	3	3	2	3	2	4	0	17
B=4t		 0	N	3	2	3	1	2	3	1	15
			O	1	0	1	0	0	0	0	2
			NO		1	2	1	—	—	—	4
			N_2O					1	4	1	6
			NO_2					0	1	1	2
			Σ	4	3	6	2	3	8	3	29
			ΣΣ	75	93	99	51	106	243	46	713
						243			395		

[a] As in Table 1 with hydrogen atoms (v = 1) in all possible locations.
[b] Hetero-atoms (Z) as in Table 1, excluding hydrogens atoms.
[c] Number and orientation of hetero-atoms (other than hydrogen).

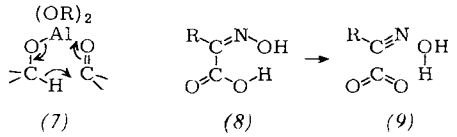
The simplest pericyclic reaction, $B=0(H_6)$, appears to be the preferred reaction path for hydrogen scrambling, the high entropy of organizing three hydrogen molecules into a six-electron cyclic transition being offset by the stabilization gained[10].

The combinations with v = 1 sites have been handled separately in Table 2, which shows those shells B > 1 containing v = 1 sites (circled in Table 1) reproduced in their several combinations with H occupying v = 1 sites. The variations possible with v = 2 (O) and v = 3 (N) substitution of the remaining sites are then tabulated under Z_1, Z_2, and Z_3.

The total number of permutations of shells and atoms in the six-atom/six-electron set is not available from a simple formula owing to the varying symmetries of the thirteen shells and the atom combinations, as well as the limitations imposed on valency possibilities by the shells. However, the major collection of C_5Z, C_4Z_2, and C_3Z_3 in Table 1 with the v = 1 possibilities in Table 2 (and the 13 C_6 cases) yields a total of 1683 formally possible reactions: with the nonlisted, presumably much less viable cases (C_2Z_4, CZ_5, *etc.*) the number will easily be over 2000. Furthermore, there are similar galaxies of pericyclic reactions derivable from other sets of $4n+2$ electrons on frames of various numbers of atoms, the five-atom/six-electron set being explored in detail below. Such collections are reminiscent of the varieties of structure available to heterocyclic molecules, and a sensible anthology of known reactions would best be treated in a survey of reactions comparable to the Ring Index[11] for heterocyclic molecular structures.

To facilitate description and comparison of pericyclic reactions, now often buried in obscure and difficultly retrievable literature descriptions, we require a simple categorizing nomenclature based on shell and atom-combination variations. (Simplicity must be emphasized because of the multitude of reactions requiring mutual discrimination.) If the shell is annotated by B, the atom combinations can be simply listed in parentheses as above, the total number of atoms being thereby implicit, *e.g.* $(C_4Z_2)=(C_4N_2)$, (C_4NO), (C_4OH), *etc.* for six-atom cases, $(C_3Z_2)=(C_3O_2)$, (C_3NH), *etc.*, for five-atom cases. The permutations of position for these atoms are most easily handled by subscripting the letter symbol for orientation of any subset of like atoms, either carbons or heteroatoms as a group, as with $(C_4NO)_P$ indicating *para*-orientation of NO or $(C_2N_4)_M \equiv (C_2N_4)_T$ for *meta*-placed carbons, the equivalent of four nitrogens oriented "T". The added subscript for these permutations may be regarded as optional and is anyway unnecessary for C_5Z or CZ_5. This single subscript is simple and offers a valuable subset breakdown for most cases, but it is inadequate to describe fully the complete orientation of atoms either among themselves in complex cases like $(C_3NOH)_L$ or with respect to their orientation on the shell in others. On the other hand a fully sufficient but more complex notation will probably be too unwieldy to learn and use. An initial catalog of known pericyclic reactions culled from the literature is appended to this article, organized on the above format.

For purposes of focusing only on the unity of the general reaction and its varietal possibilities, we shall ignore considerations of the concerted nature of these reactions required by orbital symmetry conservation[1]; in many cases such mechanistic facts are unknown anyway. If we do this we see that many reactions commonly thought about in other contexts fit into our pattern. Thus, while all-carbon analogs (or C + H) of shells below B = 3 appear to be unknown (unless we accept hydrogen transfer as $B=2_P$ $(C_4H_2)_P$ and catalytic allylic hydrogen exchange as $B=2_O$ $(C_3H_3)_V$, there are a number of cyclic reactions containing heteroatoms that may be included, such as the Meerwein-Ponndorf-Verley reduction and Oppenauer oxidation with $B=2_P$ $(C_2MO_2H)_M$ (cf. *(7)*), or its analogs with other metals, the Cannizzaro and Leuckart reactions, and the thermal fragmentation of α-hydroxyimino acids *(8)*→*(9)*; $B=2_M$ $(C_2NO_2H)_O$) as well as a number of other pyrolytic decarboxylations.



(7) *(8)* *(9)*

The possible variations in the shell of the generalized pericyclic reaction are large but finite. The present tabulation allows

the possible reactions to be encompassed and examined in detail with a view to discovering new reactions of potential utility and observing the scope of others not fully explored. The main reactions with some precedent to date are largely those with fuller shells ($B \geq 3$) and chiefly carbon skeletons (or C + H), in particular $B = 3_L$, 4_X, 4_T, 4_U, and 5.

An approximate calculation of the energy difference between two partners may be made to ascertain the preferred direction of reaction. This is quickly accomplished as the difference between the bond energies of the three bonds made and the three broken. Approximate bond energy values are given in Table 3 in the form most useful for this purpose, with the "π" column indicating the net energy change on going from triple to double or double to single bond, and the "σ" column the energy of single bonds. Except for halogens, bond energies generally vary with chemical environment and so the averages shown are rounded off for easier calculation, but equilibrium preferences under about 20 kcal/mol must be regarded as suspect[12].

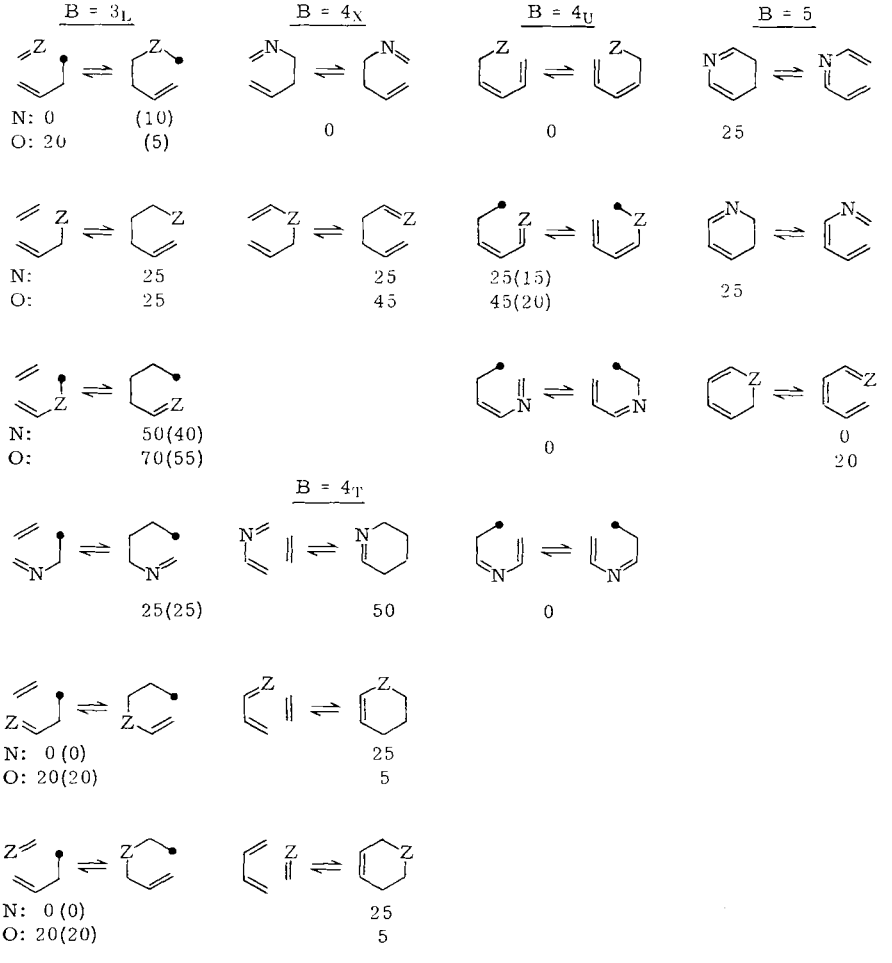
The monosubstituted (C_5Z) examples of these five classes are collected in Scheme 1, 29 combinations on 18 skeletons with substituted $v = 2$ sites labeled as Z(= N or O) and $v = 3$ sites labeled as N. The sites marked with heavy dots represent $v = 1$ sites (in 4_U and 3_L) and may be separately regarded as occupied by C or, more likely, by H. The calculated energy preferences are shown below the more stable form, labeled for Z = N or O. In cases with $v = 1$ sites the first number shown is that for the case of the transferred atom as carbon; the number in parenthesis is the energy preference if the transferred atom is hydrogen instead of carbon.

Table 3. Approximate bond energy changes [kcal/mol] [12].

	π	σ
C—C	60	85
C—N	75	75
C—O	100 (90) [a]	80 (90) [a]
N—N [b]	125	
	60	40
N—O	90	50
O—O	85	35
C—H		95
N—H		95
O—H		105 (120) [c]
C—Cl		82
C—Br		69
C—J		53
H—Cl		103
H—Br		88
H—J		71
three-membered ring [c]		30

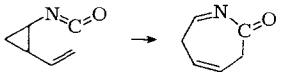
[a] Value for C—OH.
[b] First π-value for $N{\equiv}N \rightleftharpoons N{=}N$; second value for $N{=}N \rightleftharpoons N{-}N$.
[c] Value for HO—H.
[d] Approximate strain release.

There are few authentic examples of known thermal reactions[13] from these 29 combinations (42 combinations with transfer atom as H as well as C). The most studied is the



Scheme 1. Combinations of C_5Z in higher shells. Calculated energy preferences [12] shown under favored form in kcal/mol (Z = N or O). Heavy dot = σ-transfer atom: first listed energy for C, in parenthesis for H.

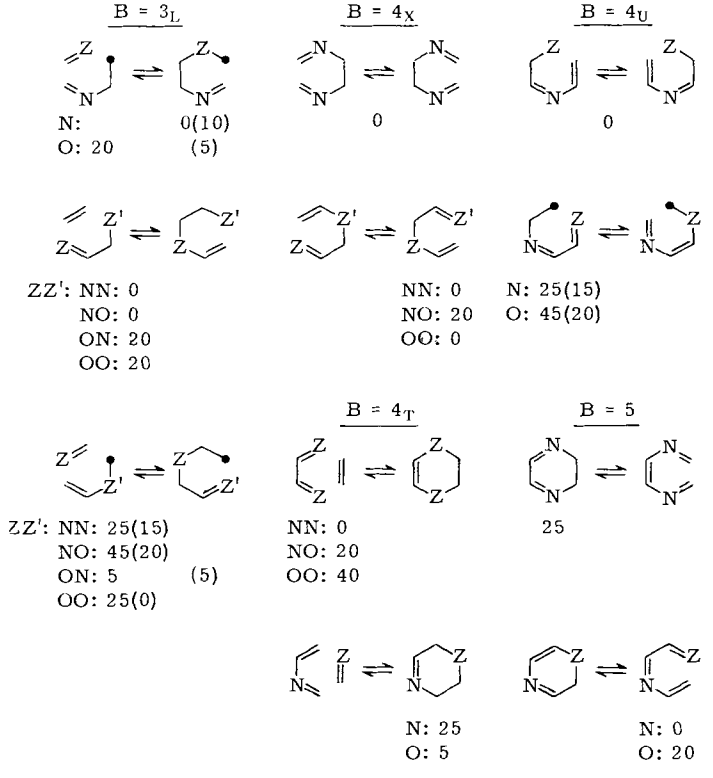
Claisen rearrangement[14], $B=4_X$ (C_5O). In this case as in many others the clear thermodynamic preference apparently derives mainly from the energy released on formation of the carbonyl group. An example of the other $B=4_X$ reaction (C_5N) is known[17] in which the starting imine is incorporated in an isocyanate and the driving force is provided by opening a cyclopropane (*(10)→(11)*). The reaction may be capable of further extension in other instances in which its potential synthetic utility in forming a C—C bond could be exploited.



(10) *(11)*

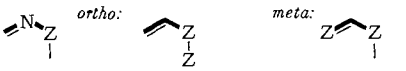
Cases of "hetero-substituted" [4+2] cycloadditions ($B=4_T$) have been systematically reviewed[15]; only the first of the three cases tabulated (Scheme 1) appears to be without reported examples. The cracking of enol and ynol ethers[18] exemplifies the fifth case of $B=3_L$ and a complex example of the second $B=5$ skeleton has been reported[19] in which the starting imine is again an isocyanate.

The much larger group of C_4Z_2 examples needs more reorganization to appreciate easily. The numbers of atom combinations for shells $B=3_L$, 4_X, 4_T, 4_U, and 5 total 121. The number of *para*-oriented heteroatom cases is the least (26 cases on 11 σ-skeletons) and is fully tabulated in Scheme 2. Again the number of known cases is relatively few.



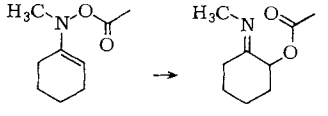
Scheme 2. Combinations of *para*-C_4Z_2 in higher shells (cf. Scheme 1).

The *ortho*- and *meta*-oriented heteroatom examples are greater (49 *ortho* and 46 *meta*) but a perusal of these shows certain cases to be more interesting, in part because the precursors are more easily created. These cases include as *ortho* examples hydrazones, oximes and their enolized tautomers, and as *meta* examples the set of Z=C—Z compounds, *i.e.* the family of carboxylic acid derivatives. The selected cases are all characterized by exhibiting an obligatory partial shell of two adjacent *(ortho)* bonds, as shown below.



hydrazones oximes — vinylhydrazines and -hydroxylamines — esters etc.

This limitation selects 16 of the 19 *ortho* σ-skeletons, leaving out saturated hydrazines (two cases of $B=3_L$) and the three Diels-Alder reactions with Z=Z dienophiles ($B=4_T$). The latter are well documented[15] in the cases of oxygen, azo compounds such as azodicarboxylic acid derivatives, and nitroso compounds acting as dienophiles. Of the 18 *meta* skeletons only 7 are included, *i.e.*, those in which the shell itself links the two *meta* heteroatoms. This omits mainly cases of acetals (and their nitrogen analogs), Z—C—Z, in either reactant species. This selection of 7 *meta* and 16 *ortho* skeletons, while somewhat arbitrary, apparently includes virtually all the known examples (except the cycloadditions noted above for Z=Z). Scheme 3 illustrates the 54 cases thus selected from the 95 *ortho*- and *meta*-heteroatom examples. The calculated energy preferences are tabulated separately in a parallel Scheme 3A. Recognizable as known reactions are the strongly preferred $B=4_X$ vinylhydrazines, variants of the Cope rearrangement, which include the Fischer indole synthesis $(C_4N_2)_O$ and the $(C_4NO)_O$ analogs reviewed by *Hill et al.*[20]; another example is the α-acetoxylation of ketones, *((12)→(13))*[21].



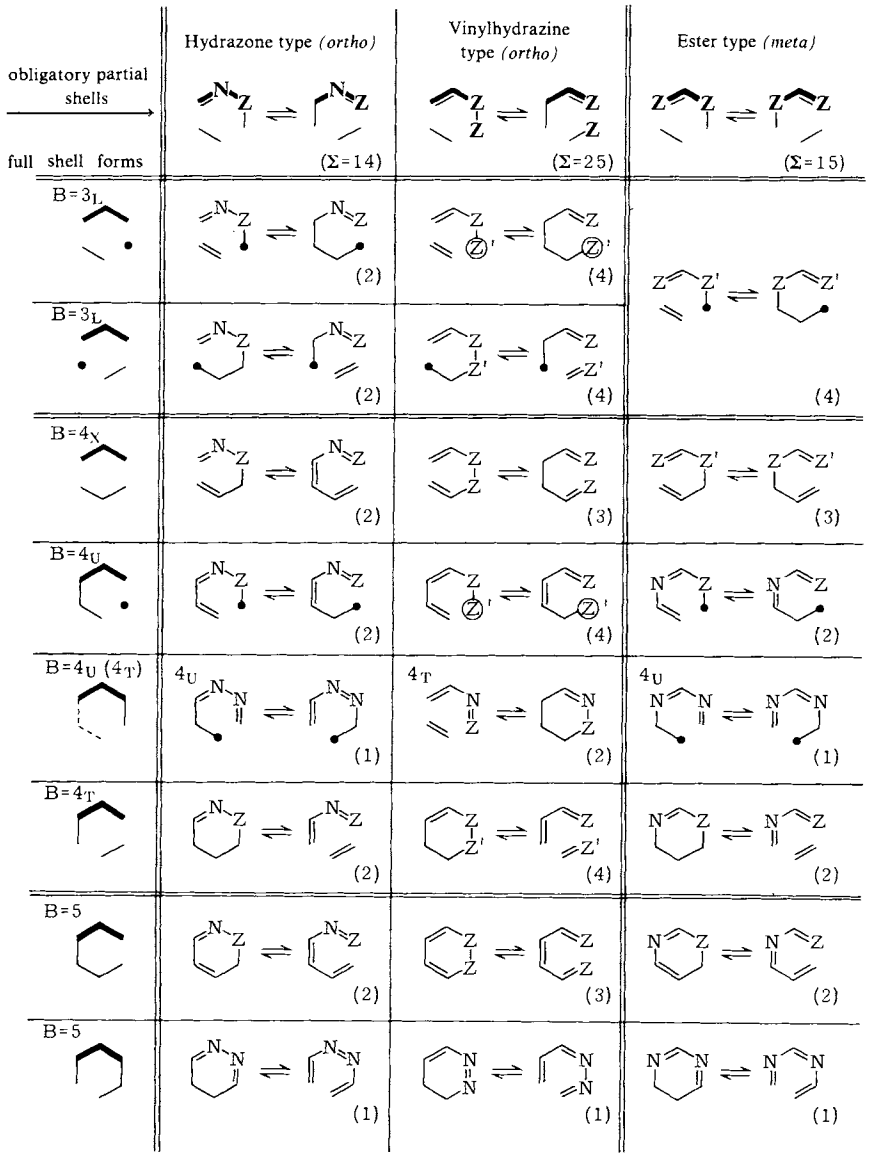
(12) *(13)*

Other examples are the family of ester pyrolysis elimiminations (Scheme 3, ester type; $B=3_L$ $(C_3O_2H)_L$, $(C_3OSH)_L$, $(C_3NOH)_L$, *etc.*). Of these, imino ether pyrolysis would appear to be the most promising of the four eliminations. The ester types also include allylic rearrangements ($B=4_X$).

The "ene reaction" ($B=3_L(C_5H)$) shows an equilibrium preference for the cycloaddition direction, but the reverse fragmentation proceeds with facility at room temperature in the second vinylhydrazine case in Scheme 3 ($B=3_L$ $(C_3NOH)_L$[22]). As calculated, the reaction direction is reversed here, largely because of cleavage of the weak N—O bond.

3. The Five-Center Model

The basic definition of the common thermal pericyclic reaction requires three pairs of electrons in a cyclic transition, but not necessarily six atoms. Hence rings with numbers of atoms other than six may be considered for the cycle, as they are considered for parent aromatics. The most common parent aromatic is the five-atom frame, exemplified in cyclopentadienyl anion, pyrrole, furan, thiazoles, imidazole, tetrazole, *etc.* The seven-atom frame is the six-electron aromatic, tropylium ion, from which a set of seven-atom/six-electron pericyclic reactions can be generated with fewer σ bonds in the shell.



Scheme 3. Selected *ortho*- and *meta*-C_4Z_2 with partial shells $B_0=2_O$.

Scheme 3 A. Calculated energy preferences for the examples in Scheme 3.

Shell	Hydrazone type *(ortho)*			Vinylhydrazine type *(ortho)*				Ester type *(meta)*			
$B=3_L$	Z	N	N	N	N	O	O	N	N	O	O
	Z′	N	O	N	O	N	O	N	O	N	O
		20	50	75	70	**90**	110	25	45	5	25
		(10)	(40)					(15)	(0)	(−5)	(0)
$B=3_L$	Z	N	N	N	N	O	O	—	—	—	—
	Z′	N	O	N	O	N	O	—	—	—	—
		−30	−5	50	65	65	105	—	—	—	—
		(−30)	(−5)	(50)	(65)	(65)	(105)		—	—	—
$B=4_X$	Z	N	N	N	N	O		N	N	O	
	Z′	N	O	N	O	O		N	O	O	
		−5	45	75	90	130		0	20	0	
$B=4_U$	Z	N	N	N	N	O	O	N	N		
	Z′	N	O	N	O	N	O	N	O		
		−5	20	50	45	65	85	25	45		
		(−15)	(5)					(15)	(20)		
$B=4_U/4_T$	(4_U)	−50		(4_T)	N	O		(4_U)	O		
		(−50)			55	30			(0)		
$B=4_T$	Z	N	N	N	N	O	O	N	N		
	Z′	N	O	N	O	N	O	N	O		
		−55	−5	25	40	40	80	−25	−5		

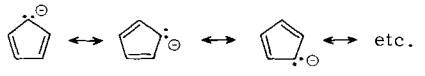
Table 3A. (continued)

Shell	Hydrazone type *(ortho)*			Vinylhydrazine type *(ortho)*			Ester type *(meta)*	
B=5	Z	N	N	N	N	O	N	N
	Z'	N	O	N	O	O	N	O
		−30	−5	50	65	105	0	20
B=5		−55			5		−25	

[a] Equilibrium preference is as written (to the right) for positive values, to the left for negative [12]. Energies in parenthesis are for σ-transfer of H.

Similarly, four-atom/six-electron aromatics may be conceived, along with a galaxy of related pericyclic reactions. The seven-atom frame suffers more in entropy considerations for cycloaddition variations and is not treated here, while the four-atom frame suffers from bond-angle constraints and is also not explored.

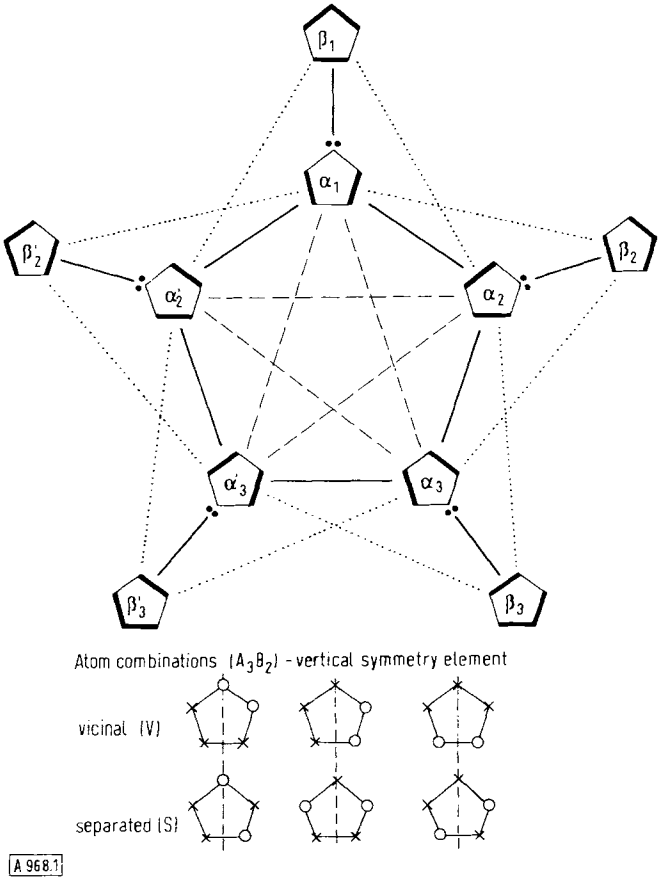
The five-atom, or pentagonal, cases may be constructed from the six-atom (hexagonal) cases above by replacing two atoms linked with a shifting bond with one atom bearing an unshared pair to be involved in the transition. This creates a basic set of a cycle of five atoms containing two bonds and an unshared pair, as in the full-shell (B=5) exemplar of aromatic resonance, cyclopentadienyl anion *(14)* and its hetero-substituted analogs, the 33 possible five-membered neutral heterocyclic aromatics (with N, O, S; O and S count as v=3 in Table 4 since some forms involve $=O^{\oplus}-$ and $=S^{\oplus}-$).



(14)

The symmetry of the basic electron set is lower—one symmetry element (plane or axis) rather than three. Accordingly there are five forms (instead of two) through which the six shifting electrons pass to return to a starting orientation, the symmetry element rotating through $2\pi/5$ with each shift. These are shown, as the inner ring of five forms labeled α, in Figure 1. Each one of the α-forms may also shift to a corresponding β-form, with three bonds and the same symmetry element, as shown. The β-forms correspond to the second species in a six-atom shift with two atoms formally replaced by one as noted above. The α⇌β equilibrium is also a six-electron pericyclic shift and involves a valency change at the one atom bearing the unshared pair in the α-form. The α→β reaction is formally an oxidation (Δv = +1), and β→α a reduction[23]. The dotted paths in Figure 1 denote two- or four-electrons shifts, not involving the full cycle of six electrons, and commonly represent formal resonance forms (those inside the α-form circuit are four-electron shifts, *e.g.*, allylic resonance; those outside are two-electron changes).

We may now construct the (eight) possible immobile shells of σ bonds among the five cyclic atoms, as before. Again the orientations mirror those of five-ring substituent patterns, there being two orientations each for the B=2 and 3 shells and these orientations are of course complementary. The two orientations are labeled *vicinal* (V)—corresponding to $B=2_O$ or 3_V in the six-rings—and *separated* (S). Hence the eight shell combinations are B=0, 1, 2_V, 2_S, 3_V, 3_S, 4, and 5. All of these shells have one symmetry element and only B=0 and 5, with full fivefold symmetry, have more. In superimposing



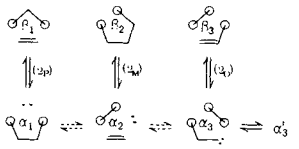
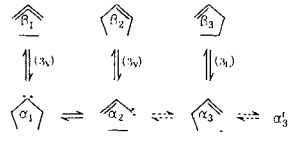
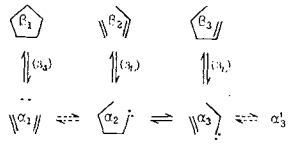
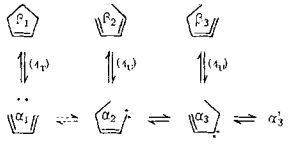
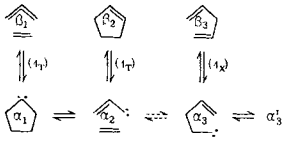
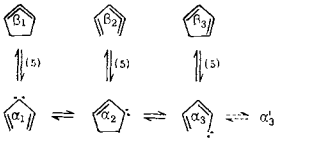
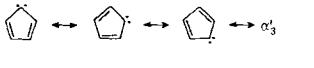
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Fig. 1. Transformation pathways among five-ring forms.

the shells on the shifting electron net we obtain for each case (except B=0 and 5) only three identifiably different ring positions and only six of the ten forms of Figure 1 remaining unique. These pentagonal shells (with vertical symmetry elements) are presented with the six equilibrating forms for each in Table 4, following the format of Table 1 for hexagonal shells. The list of valencies for each is a clockwise reading of v_i from the top atom on the symmetry element of the shell and is the list for the α-forms only, as the β-forms each have one atom of higher valency.

On the α⇌β arrows are noted in parentheses the corresponding form in the hexagonal series derived by formal replacement of the atom with the unshared electron pair in the pentagonal α-form with two atoms linked by a double bond in the hexagonal frame; the same atom in the pentagonal β-form is hence replaced by two atoms linked by a single bond in order to become the corresponding hexagonal reaction partner. In this formal correspondence the pentagonal B=5 corresponds to the hexagonal B=6, *i.e.* aromatic resonance. Furthermore, certain inter-α transformations are shown with dashed equilibria, which is to imply that that reaction is

Table 4. Combinations of five-center thermal pericyclic reactions ($\alpha \rightleftharpoons \alpha'$).

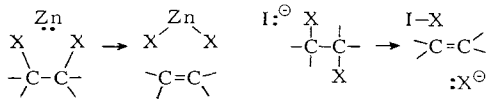
Shell	Reactions [a]	Atoms [b]	C_4Z	C_3Z_2 [c] V	C_3Z_2 [c] S	C_2Z_3 [c] V	C_2Z_3 [c] S	CZ_4	Σ
B=1		N	3	3	3	3	3	3	18
		O	3	3	3	3	3	3	18
		NO		5	5	—	—	—	10
(11221)		N_2O				8	8	—	16
		NO_2				8	8	—	16
		N_3O						10	10
		N_2O_2						16	16
		NO_3						10	10
		Σ	6	11	11	22	22	42	114
B=2V		N	3	3	3	3	3	3	18
		O	2	2	2	1	1	1	9
		NO		4	4	—	—	—	8
(32112)		N_2O				6	6	—	12
		NO_2				5	5	—	10
		N_3O						8	8
		N_2O_2						10	10
		NO_3						4	4
		Σ	5	9	9	15	15	26	79
B=2S		N	3	3	3	3	3	3	18
		O	3	3	3	3	3	3	18
		NO		5	5	—	—	—	10
(12222)		N_2O				8	8	—	16
		NO_2				8	8	—	16
		N_3O						10	10
		N_2O_2						16	16
		NO_3						10	10
		Σ	6	11	11	22	22	42	114
B=3V		N	3	3	3	3	3	3	18
		O	2	1	1	1	0	0	5
		NO		3	3	—	—	—	6
(12332)		N_2O				5	5	—	10
		NO_2				3	2	—	5
		N_3O						6	6
		N_2O_2						5	5
		NO_3						1	1
		Σ	5	7	7	12	10	15	56
B=3S		N	3	3	3	3	3	3	18
		O	2	2	2	1	1	1	9
		NO		4	4	—	—	—	8
(32222)		N_2O				6	6	—	12
		NO_2				5	5	—	10
		N_3O						8	8
		N_2O_2						10	10
		NO_3						4	4
		Σ	5	9	9	15	15	26	79
B=4		N	3	3	3	3	3	3	18
		O	1	1	0	0	0	0	2
		NO		2	2	—	—	—	4
(33223)		N_2O				3	3	—	6
		NO_2				1	1	—	2
		N_3O						4	4
		N_2O_2						2	2
		NO_3						0	0
		Σ	4	6	5	7	7	9	38
B=5		N	1	1	1	1	1	1	6
		O	0	0	0	0	0	0	0
(33333)		Σ	1	1	1	1	1	1	6
		ΣΣ	32	54	53	94	92	161	486

[a] Circled atoms transferred *via* σ-bonds; minimum obligatory valencies in parentheses (cf. Table 1); numbering starts from the top center atom on the vertical symmetry element.

[b] N, O are generalized for v=3 and v=2 atoms, respectively.

[c] Orientation of the hetero-atom Z is shown.

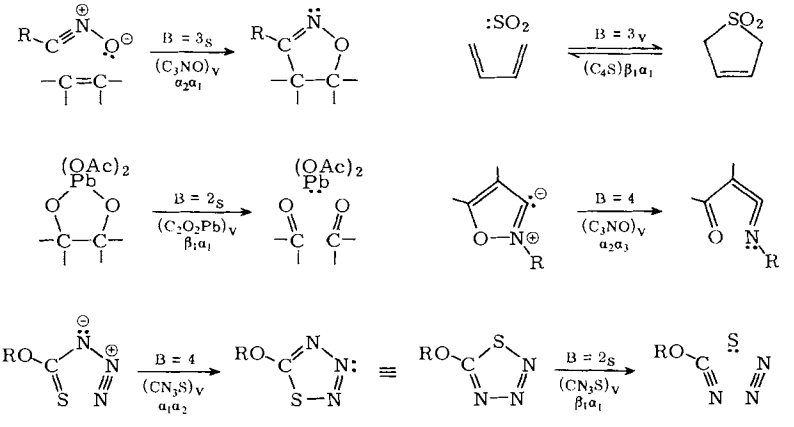
equally viable for the six electrons in a linear fashion, *i.e.*, does not require a cyclic transition state[24]. This occurs in any shift in which the atom bearing the unshared pair in one partner is not linked by a shell bond to that containing the pair in the other partner. By contrast, all $\alpha \rightleftharpoons \beta$ shifts have obligatory cyclic transitions. This may be illustrated by observing a possible six-electron cyclic mechanism for the reaction of zinc with *cis*-dibromides yielding the corresponding olefin as an example of B=1 ($C_2X_2Zn/\alpha_1\beta_1$)[26], *(15)*, and comparing it with the linear *trans*-elimination mechanism of the otherwise analogous iodide-initiated elimination, *(16)*, which is a *trans*, non-cyclic version of B=1 ($C_2X_3/\alpha_1\alpha_2$).



(15) (16)

In substituting different atoms into the pentagonal shells we note first the valency change at one atom ($\Delta v = \pm 1$) in the $\alpha \rightleftharpoons \beta$ interconversions, which lays restrictions on the kinds of groupings acceptable at those atoms. The major such groupings are listed for the three different valency conditions in Table 5. Owing to the greater number (six) of possible interconversions in the pentagonal shells and the valency change limitations at one site for the $\alpha \rightleftharpoons \beta$ interconversions, a tabulation of atom or group combinations on each shell is less clearly constructed. In most cases a given heteroatom-substituted shell will not be capable of most of the six equilibria; indeed in many cases only one will be viable. The table of N/O atom combinations (+C) is presented as before, nevertheless, and derived for the valencies of the α-forms (Table 4). A second table (Table 6) is presented for combinations with one atom present (Q) capable of the $\alpha \rightleftharpoons \beta$ valency change; it may occupy any of three sites on any shell (excluding B=0 and 5), and the site it occupies dictates which of the three $\alpha \rightleftharpoons \beta$ transformations is viable for that species. Hence Table 6 is organized to show C_3QZ (Z=N or O), C_2QZ_2, and C_1QZ_3 for each position of Q (note that there are three C_4Q species also for each shell). The atoms Q are those of Table 5, undistinguished here as to valency since the same atoms tend to appear in all three valency lists in Table 5.

In general it may be observed, in simplification of Table 6, that each box for one shell with Q in one position tabulates the successive restrictions in variety as oxygens are substituted owing to the number of v=3 sites which it may not occupy. The first line, for nitrogens only, shows the substitution at any position by nitrogens and hence the maximum variety of single atom substitution. As the first column of boxes represents a form with symmetry, the numbers are smaller and are always $C_3QN=2$, $C_2QN_2=4$, $CQN_3=2$ or 8 ways to substitute nitrogens while the two asymmetric placements of Q are greater (and alike) as $C_3QN=4$, $C_2QN_2=6$, $CQN_3=4$, or 14 ways in each to substitute nitrogens. The totals are placed in parenthesis for each box. Since oxygen may occupy either v=1 or 2 sites, some shells show the same number of combinations, *e.g.* B=1 and B=2S, but in general, as the shells become larger (thus increasingly excluding oxygen), the number of combinations decreases, as in the hexagonal series above.



Scheme 4. Examples of pericyclic five-center reactions.

Table 5. Atoms or groups capable of valency change ($\Delta v = \pm 1$).

v=1 ⇌ 2		v=2 ⇌ 3		v=3 ⇌ 4	
α	β	α	β	α	β
C:	C	C	C *	C	C *
(O=C ⇌ O=C)					
N:	N: *	N:	N *		
N+	N+ *	N+	N+ *	N+	N+ *
P:	P:	P (O,S)	P (O,S) *		
S:	S:	S:	S: *	S (O)	S (O) *
:SO2	SO2	S (O)	S (O) *		
M	M				

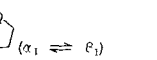
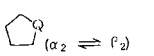
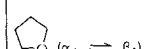
Note: * denotes thermodynamically preferred partner.

Common examples of these various pentagonal frame pericyclics will include those in Scheme 4. Only one of the many examples of 1,3-dipolar cycloaddition[27] is illustrated for $B=3_S$ while the cycloaddition of sulfur dioxide to dienes[28] ($B=3_V$) is also known in reverse as the analogous fragmentation of CO from bridged olefinic ketones[29]. Lead tetraacetate (and periodate) cleavage of glycols, amino alcohols, *etc.*, is shown for $B=2_S$, and B=4 is illustrated by *Woodward*'s isoxazolium reagent[30]. In each case the frame is oriented with the shell symmetrically placed on a vertical axis as in Tables 4 and 6. The two consecutive reactions of thioacyl azides included are especially noteworthy illustrations of the possible variations[31].

4. Other Pericyclic Systems

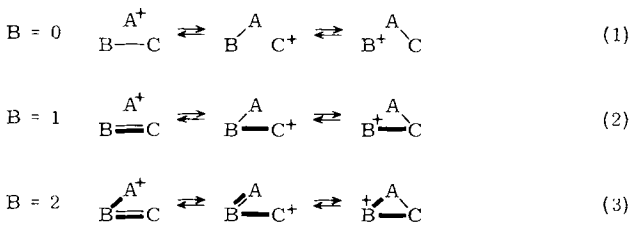
The simplest formal set of pericyclic reactions is that based on the $(4n+2=2)$-electron aromatic, cyclopropenium ion, *i.e.*, a two-electron/three-atom system for which the full shell is B=3, the aromatic cation itself. The shells are characterized

Table 6. Combinations of five-center thermal pericyclic reactions ($\alpha \rightleftharpoons \beta$).

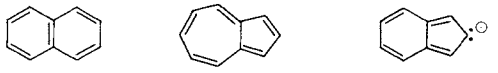
Shell																	Totals					Σ
		C_3QZ	C_2QZ_2 V	C_2QZ_2 S	CQZ_3 V	CQZ_3 S	C_3QZ	C_2QZ_2 V	C_2QZ_2 S	CQZ_3 V	CQZ_3 S	C_3QZ	C_2QZ_2 V	C_2QZ_2 S	CQZ_3 V	CQZ_3 S	C_3QZ	C_2QZ_2 V	C_2QZ_2 S	CQZ_3 V	CQZ_3 S	
B=1 	N	2	2	2	1	1	4	3	3	2	2	4	3	3	2	2	10	8	8	5	5	36
	O	2	2	2	1	1	4	3	3	2	2	4	3	3	2	2	10	8	8	5	5	36
	NO		3	3	–	–		6	6	–	–		6	6	–	–		15	15	–	–	30
	N_2O				3	3				6	6				6	6				15	15	30
	NO_2				3	3				6	6				6	6				15	15	30
	Σ	4	7	7	8	8	8	12	12	16	16	8	12	12	16	16	20	31	31	40	40	
	ΣΣ	4		14 (34)		16	8		24 (64)		32	8		24 (64)		32	20		62		80	162
$B=2_V$ 	N	2	2	2	1	1	4	3	3	2	2	4	3	3	2	2	10	8	8	5	5	36
	O	2	2	2	1	1	3	2	1	1	0	3	1	2	0	1	8	5	4	2	2	22
	NO		3	3	–	–		5	4	–	–		4	5	–	–		12	12	–	–	24
	N_2O				3	3				5	4				4	5				12	12	24
	NO_2				3	3				4	2				2	4				9	9	18
	Σ	4	7	7	8	8	7	10	8	12	8	7	8	10	8	12	18	25	25	28	28	
	ΣΣ	4		14 (34)		16	7		18 (45)		20	7		18 (45)		20	18		50		56	124
$B=2_S$ 	N	2	2	2	1	1	4	3	3	2	2	4	3	3	2	2	10	8	8	5	5	36
	O	2	2	2	1	1	4	3	3	2	2	4	3	3	2	2	10	8	8	5	5	36
	NO		3	3	–	–		6	6	–	–		6	6	–	–		15	15	–	–	30
	N_2O				3	3				6	6				6	6				15	15	30
	NO_2				3	3				6	6				6	6				15	15	30
	Σ	4	7	7	8	8	8	12	12	16	16	8	12	12	16	16	20	31	31	40	40	
	ΣΣ	4		14 (34)		16	8		24 (64)		32	8		24 (64)		32	20		62		80	162
$B=3_V$ 	N	2	2	2	1	1	4	3	3	2	2	4	3	3	2	2	10	8	8	5	5	36
	O	1	0	1	0	0	2	1	0	0	0	3	2	1	1	0	6	3	2	1	0	12
	NO		2	1	–	–		3	3	–	–		5	4	–	–		10	8	–	–	18
	N_2O				1	2				3	3				5	4				9	9	18
	NO_2				0	1				1	1				4	2				5	4	9
	Σ	3	4	4	2	4	6	7	6	6	6	7	10	8	12	8	16	21	18	20	18	
	ΣΣ	3		8 (17)		6	6		13 (31)		12	7		18 (45)		20	16		39		38	93
$B=3_S$ 	N	2	2	2	1	1	4	3	3	2	2	4	3	3	2	2	10	8	8	5	5	36
	O	2	2	2	1	1	3	2	1	1	0	3	1	2	0	1	8	5	5	2	2	22
	NO		3	3	–	–		5	4	–	–		4	5	–	–		12	12	–	–	24
	N_2O				3	3				5	4				4	5				12	12	24
	NO_2				3	3				4	2				2	4				9	9	18
	Σ	4	7	7	8	8	7	10	8	12	8	7	8	10	8	12	18	25	25	28	28	
	ΣΣ	4		14 (34)		16	7		18 (45)		20	7		18 (45)		20	18		50		56	124
B=4 	N	2	2	2	1	1	4	3	3	2	2	4	3	3	2	2	10	8	8	5	5	36
	O	1	1	0	0	0	2	1	0	0	0	1	0	0	0	0	4	2	0	0	0	6
	NO		2	1	–	–		3	3	–	–		1	2	–	–		6	6	–	–	12
	N_2O				2	1				3	3				1	1				6	5	11
	NO_2				1	0				1	1				0	0				2	1	3
	Σ	3	5	3	4	2	6	7	6	6	6	5	4	5	3	3	14	16	14	13	11	
	ΣΣ	3		8 (17)		6	6		13 (31)		12	5		9 (20)		6	14		30		24	68
Totals	Σ	22	37	35	38	38	42	58	52	68	60	42	54	57	63	67	106	149	144	169	165	
	Σ	22		72		76	42		110		128	42		111		130	106		293		334	733
	ΣΣ			(170)					(280)					(283)								

by three forms, with the charge on each atom by analogy with the five-atom cases above, and the lower shells are shown in equations (1) to (3). The B=1 shell includes olefin protonation and the Wagner-Meerwein rearrangements while B=2 characterizes cyclopropyl tosylate solvolysis[32].

Much more complex sets can in principle be generated from the ten-electron aromatics. Here there can be in the potential pericyclic reactions not only the many shell combinations up to B=10 having all shell bonds on the periphery with the shifting electrons, but also combination with shell bonds

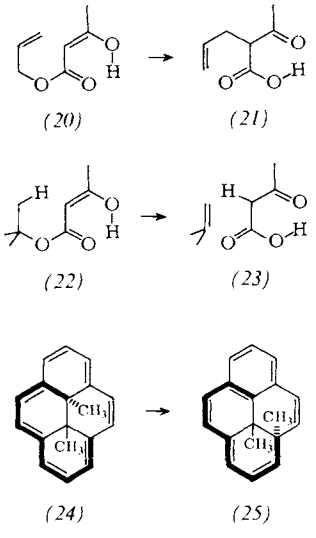


crossing the outer electron periphery as they do in naphthalene *(17)* and azulene *(18)*.



(17) *(18)* *(19)*

Examples appear to be available in the rearrangement of allyl acetoacetates (*(20)*→*(21)*) or pyrolytic elimination of tertiary acetoacetate esters (*(22)*→*(23)*)[33] with shells B=6 and B=5, respectively, including in each case the crossing or bridging shell bond of naphthalene. A sigmatropic rearrangement (σ-transfer of carbon) has been reported[5] (*(24)*→*(25)*, B=8 (C_{10})).



(20) *(21)*

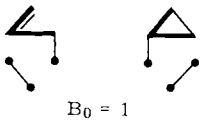
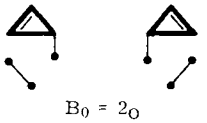
(22) *(23)*

(24) *(25)*

Furthermore, the ten-electron pericyclics do not require a frame of ten atoms as in these cases, since the aromatic indenyl anion *(19)* provides a basis for a nine-atom set in the six-electron series.

The presence of shell σ bonds across the mobile-electron periphery in naphthalene and the related ten-electron pericyclics serves to introduce the question of such bonds in the more familiar six-electron cases. A cross-bond can be laid on a hexagonal frame either to form a triangle (*meta*-connected) or a quadrangle (*para*-connected). Because of severe bond distortion in the latter skeleton its analysis is left out here. The *meta*-connected cross-bonds can be incorporated into three partial shells defining the three-membered ring part of the frame, shown in Scheme 5 labeled with the notation of the partial standard peripheral shell required. The first is a set of cases incorporating a simple 1,2-shift into the pericyclic transition; the second is an interconversion of allyl and cyclopropyl skeletons; and the third can be discarded from practical consideration as an allylic rearrangement within a cyclopropene.

Scheme 5. Shells incorporating cross-bonds in a six-center model.

	Numbers of unique placements on standard shells		
 $B_0 = 0$	B=0 (1) B=1 (2) B=2_O (2) B=2_M (1)	B=2_P (1) B=3_L (1) B=3_V (1) B=4_U (1)	
Rearrangement of A			Σ=10
 $B_0 = 1$	B=1 (1) B=2_O (1) B=2_M (2) B=2_P (1) B=3_Δ (1) B=3_L (4)	B=3_V (1) B=4_X (1) B=4_T (2) B=4_U (1) B=5 (1)	
Allyl-cyclopropyl shift			Σ=16
 $B_0 = 2_O$	B=2_O (1) B=3_L (1) B=3_V (1) B=4_X (1)	B=4_T (1) B=4_U (2) B=5 (2)	
Cyclopropene			Σ=9 Total =35

The number of unique ways in which a *meta*-connected cross-bond can be attached to each of the thirteen standard peripheral shells equals the number of unique sites on that shell marked in Table 1. These fall into the three partial shell sets as enumerated in Scheme 5 beside each set. The first set (rearrangement of A) is more clearly seen and easily enumerated as a pentagonal frame with the rearranging group, A, understood as bonded to the unshared electron pair which shifts to the adjacent site (Fig. 1, α⇌α'). The example shown in Scheme 6 is the simplest rearrangement frame and corresponds to the $\alpha'_3 \rightleftharpoons \alpha_3$ reaction for B=1 and is identical with a cross-bond on a B=0 hexagonal frame. The ten rearrangements corresponding to the ten cross-bond shells of Scheme 5 are listed in Scheme 6 with the shells symmetrically placed as in Table 4. This allows the use of Table 4 to enumerate the atom combinations for these ten rearrangement shells, *i. e.*, 486 possibilities for each one[34]. Alternatively, the ten shells can be constructed from $B_O=1$ by leaving the bond across which group A migrates in its symmetrical placement as shown in Scheme 6 and subsequently adding all possible shell combinations to it so that the $\alpha'_3 \rightleftharpoons \alpha_3$ migration is maintained in all; this presentation was used for the examples in Scheme 7.

Scheme 6. Rearrangements in a five-center model.

Pentagonal shell [a]	Corresponding hexagonal shell [b]	Reaction model [c]
B=1 ($\alpha_3 \rightleftharpoons \alpha'_3$)	B=0	CF
B=2_V ($\alpha_1 \rightleftharpoons \alpha_2$)	B=1	F/C
B=2_S ($\alpha_2 \rightleftharpoons \alpha_3$)	B=1	F/C
B=3_V ($\alpha_2 \rightleftharpoons \alpha_3 \rightleftharpoons \alpha'_3$)	B=2_P; 2_O	R
B=3_S ($\alpha_1 \rightleftharpoons \alpha_2$)	B=2_M	F/C
($\alpha_3 \rightleftharpoons \alpha'_3$)	B=2_O	R
B=4 ($\alpha_1 \rightleftharpoons \alpha_2 \rightleftharpoons \alpha_3$)	B=3_L; 3_V	R
B=5 ($\alpha_1 \rightleftharpoons \alpha_2$)	B=4_U	R
 B=1 ($\alpha'_3 \rightleftharpoons \alpha_3$)		

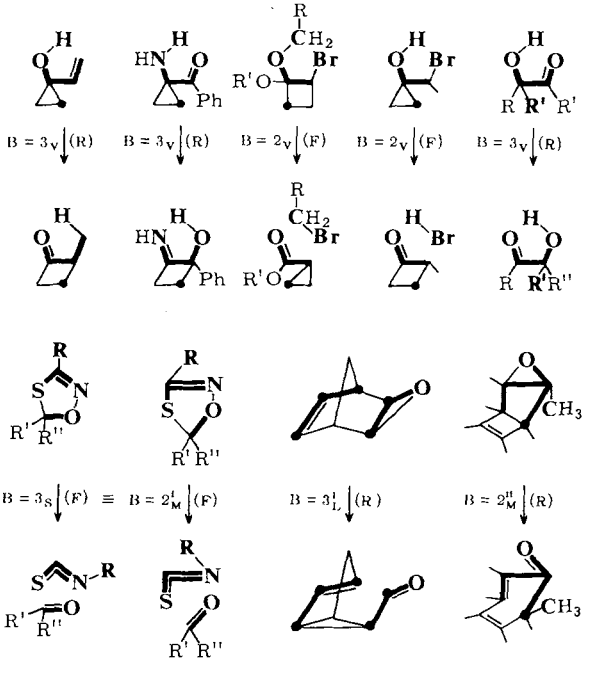
[a] Shells symmetrically placed on vertical symmetry element (as in Table 4).

[b] Six-center shell plus cross-bond: ten cases are enumerated in Scheme 5.

[c] C=cycloaddition; F=fragmentation; R=rearrangement; both forward and reverse modes are shown.

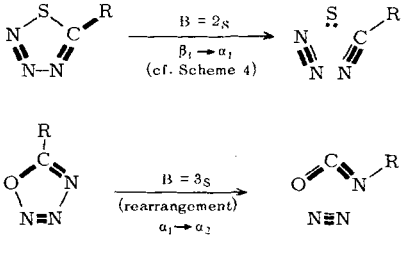
Enumeration of the atom combinations for the allyl-cyclopropyl shift set is not so easy. Translation from the hexagonal frame to the pentagonal frame necessitates a requisite shell bond out from the pentagonal frame to the sixth atom (in the three-membered ring), and this places further limitations on the possible atoms to which the sixth atom is attached, but multiplies the result by the three atoms (C, N, and O) which may be used in that sixth atom position. In any case these shells are more easily apprehended on the hexagonal frame of Scheme 5 and the 16 shells could be enumerated separately as in Tables 1 and 2, yielding lower totals because of the increased minimum obligatory valencies at the two ends of the cross-bond.

Examples of both sets are known, and they exhibit cycloaddition, fragmentation, and rearrangement modes (illustrated in Scheme 7). The first row in Scheme 7 consists of several parallel rearrangements discussed by *Conia et al.*[35]; the acyl-



Scheme 7. Examples of pericyclic reactions with cross-bonded shells.

oin rearrangement[36] is included as a possible parallel. In the second row is a fragmentation[37] written on both pentagonal and hexagonal frames as well as two three-ring openings (cyclopropyl-allyl type) with crossed bonds[38]. The second of these actually has two crossed bonds, one of each type. Equation (4) draws a parallel between the behavior of thioacyl azides[31] and acyl azides. If the latter initially rearrange on heating like the former, there is a basis for a rearrangement with fragmentation which constitutes a different possible view of the mechanism of the Curtius (and analogously, the Wolff) rearrangement as a pericyclic reaction, taking a different course



(4)

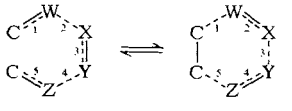
from that of the thioacyl case since sulfur can act as a "Q" atom with valency change while oxygen cannot.

5. Pericyclic Reactions in Synthesis

The very large number of formal possibilities for pericyclic reactions creates a need for imposition of a system of organization oriented to their value and potential success as useful chemical reactions. We may impose such a system based on the kinds of transformations important to synthesis. There are three such reaction families which alter skeletal carbons in synthesis, the first changing function (hetero-atom) attachments at a carbon, the other two forming (or cleaving) σ- and π-bonds, respectively, between carbons[39]:

Refunctionalization:	Y C—Z ⇌ Y—C Z
Construction/cleavage:	C C ⇌ C—C
Elimination/addition:	C—C ⇌ C=C

Each of these may be laid on the generalized six-electron shell (of five or six atoms) in the pericyclic reaction and will partially define and limit the possible combinations of shells and atoms in the set. This is illustrated by the synthetically most important construction (and reverse cleavage) reaction in equation (5) for the six-atom set, in which only five shell bonds (1—5) and four atoms (W, X, Y, Z) now remain to be defined. The elimination/addition family may be created from this set by inclusion of a single obligatory shell bond between the two carbons; this may be notated as the *minimal obligatory shell*, $B_O = 1$. Similarly, refunctionalizations are a set derived by replacing the lower carbon with a heteroatom and defining $W \neq C$.



(5)

Taking the construction set as an initial basis for exploration (which may then be adapted to the other two), we may further limit the set of possible combinations in several ways of importance to synthesis. These ways will further define atoms and shell bonds in eq. (5), and thus limit the remaining possible combinations.

As shown in Table 1 the number of molecular components involved on one side or another of the thirteen cases varies from one to three. These represent important synthetic differences and fall into six practical families or reaction modes (see Table 7). When starting material and product are each one component, the reaction is a *rearrangement* (R), electrocyclic or sigmatropic, as in $B = 4_X 4_U$, 5. When the starting material is a single molecule but the product is more than one, the reaction is a *fragmentation* (F), a synthetic opportunity for prior assembly of the two construction parts into one molecule to facilitate pericyclic transformation with a loss of an extraneous, possibly equilibrium-driving fragment. The reverse reactions are *cycloadditions* of two (C_2) or three (C_3) components into one molecule, the former a synthetically useful device for joining two synthons[40]. Common to the lower shells are reactions with two or three components on each side, labeled as *cycloaddition-fragmentations* of two or three starting components (CF_2 and CF_3, respectively). These distinctions (Table 7) characterize each pericyclic reaction and

represent different synthetic opportunities and probabilities of practical success; in the latter connection, R, F, and C_2 are the three most valuable and are necessarily found in the higher shells. The six modes may be grouped into three in terms of the number of starting molecules or components (k) in the reaction: $k=1$, R and F; $k=2$, C_2 and CF_2; $k=3$, C_3 and CF_3.

Table 7. Summary of reaction modes in six-center models.

Shell	σ-transfers [a]	Mode [b]	Code [c]
B=0	6	CF_3	CF_3-6
1	4	$CF_2 \rightleftarrows CF_3$	CF_2-4; CF_3-4
2_O	3	CF_2	CF_2-3
2_M	2	$C_3 \rightleftarrows F$	C_3-2; F-2
2_P	2	CF_2	CF_2-2
3_Δ	0	$C_3 \rightleftarrows F$	C_3-0; F-0
3_L	1	$C_2 \rightleftarrows F$	C_2-1; F-1
3_V	2	$C_2 \rightleftarrows F$	C_2-2; F-2
4_X	0	R	R-0
4_T	0	$C_2 \rightleftarrows F$	C_2-0; F-0
4_U	1	R	R-1
5	0	R	R-0

Summary [d]	Mode	Shell
$k=3$	CF_3	B=0, 1
	C_3	2_M, 3_Δ
$k=2$	CF_2	1, 2_O, 2_P
	C_2	3_L, 3_V, 4_T
$k=1$	F	2_M, 3_Δ, 3_L, 3_V, 4_T
	R	4_X, 4_U, 5

[a] Number of σ-bonded atoms transferred.
[b] Rearrangement (R); fragmentation (F); cycloaddition of two (C_2) or three (C_3) components; cycloaddition-fragmentation starting with two (CF_2) or three (CF_3) components.
[c] Label combining number of components as in "mode" [b] with numbers of atoms σ-transferred.
[d] k = number of starting material components.

A second distinction bearing on practicality is that of σ-transferred atoms (Table 1, footnote [a]). Because of their more demanding stereoelectronic requirements and the generally greater bond strengths of σ- over π-bonds, σ-transfers are relatively disfavored processes, at least with atoms other than hydrogen, and current precedent bears this out. In construction reactions [eq. (5)] it is then important to sort the possibilities with respect to whether either or both of the carbons to be bonded are σ-transferred. Again, the number of σ-transfers is a function of the shell and is also summarized in Table 7, along with a unified label code for each reaction identifying both its component mode (above) and its σ-transfers.

A third way of sorting the combinations of reactions defines the number of carbons in each of the synthons united in a construction reaction, *i.e.*, the number of carbons involved in the six-atom set of equation (5). Here we are focusing on the number of carbons in each starting synthon which are part of the six-atom pericyclic set in construction, *i.e.* a total of two to six involved carbons in the two synthon carbon skeletons. There are seven possible combinations of synthon skeleton sizes (the number of linear linked carbons in each synthon) and these lead to a linear span of $n \leq 6$ carbons in the product of the construction reaction[41]:

Product span: C_6 (1+5), (2+4), (3+3) [42]
C_5 (1+4), (2+3)
C_4 (1+3), (2+2)
C_3 (1+2)
C_2 (1+1)

This division of the possible combinations allows conceptualization of involved synthon sizes in a pericyclic construction, but does not necessarily limit the mode of reaction: the two synthons may be brought together as two components in a cycloaddition mode or may be joined prior to the pericyclic construction reaction by mutual linking to a heteroatom as would be the case with a rearrangement or fragmentation mode (*e.g.*, the Claisen rearrangement, $B=4_X(C_5O)$). It may be noted that only in those cases $(1+n)$ with one synthon employing only one involved carbon are σ-transfers of a construction carbon possible; this is a logical consequence of equation (5).

Table 8. Enumeration of six-center pericyclic reactions for construction.

Product Span	Synthon Skeleton	Shell [a]	Mode	Number [b]
C_6	6	$B_0=5$	R-0	1
	2+4	$B_0=4_T$	C_2-0	1
C_5	1+4	$B_0=3_V$	C_2-2	3*
		$B_0+1=4_T$	C_2-0	2
		4_U	R-1	2*
		$B_0+2=5$	R-0	1
		Total	4	8
(C_5Z)	2+3	$B_0=3_L$	C_2-1	3
		$B_0+1=4_X$	R-0	2
		4_T	C_2-0	2
		$B_0+2=5$	R-0	1
		Total	4	8
C_4	1+3	$B_0=2_O$	CF_2-3	9*
		$B_0+1=3_L$	C_2-1	6
			F-1	4*
		3_V	C_2-2	6*
		$B_0+2=4_X$	R-0	2
		4_T	C_2-0	4
		4_U	R-1	2*
		$B_0+3=5$	R-0	1
		Total	8	34

Table 8. (continued)

Product-Span	Synthon Skeleton	Shell [a]	Mode	Number [b]				
(C_4Z_2) 	2+2	$B_0=2_M$	C_3-2	6				
		$B_0+1=3_\Delta$	C_3-0	3				
		3_L	C_2-1	6				
		$B_0+2=4_X$	R-0	3				
		4_T	C_2-0	2				
		$B_0+3=5$	R-0	1				
		Total	6	21				
C_3 	1+2			(C_3Z_3)	(C_4Z_2) [c]			
		$B_0=1$	CF_3-4	27*	9*			
		$B_0+1=2_O$	CF_2-3	18*	6*			
		2_M	C_3-2	12*	6*			
			C_3-2	18*	6*			
		2_P	CF_2-2	12*	6*			
(C_3Z_3) or (C_4Z_2) [c]		$B_0+2=3_\Delta$	C_3-0	8	4			
		3_L	C_2-1	12	4*			
			C_2-1	4*	4*			
			C_2-1	6	3*			
			F-1	8*	4*			
		3_V	C_2-2	6*	3*			
		$B_0+3=4_X$	R-0	4	2			
		4_T	C_2-0	4	2			
			C_2-0	2	2			
		4_U	R-1	2*	2*			
		$B_0+4=5$	R-0	1	1			
		Total	16	144	64	(208)		
				(C_2Z_4)	(C_3Z_3)		(C_4Z_2) [d]	
C_2 	1+1				(X = C)	(Y = C)		
		$B_0=0$	CF_3-6	45*	27*	–	0	
		$B_0+1=1$	CF_3-4	54*	18*	18*	0	
			CF_3-4	21*	18*	–	6*	
			CF_2-4	36*	18*	12*	6*	
(Equation (5))		$B_0+2=2_O$	CF_2-3	18*	9*	6*	0	
			CF_2-3	12*	12*	6*	6*	
		2_M	C_3-2	24*	12*	12*	6*	
			C_3-2	21	12*	–	0	
			F-2	10*	8*	–	0	
		2_P	CF_2-2	24*	12*	8*	0	
		$B_0+3=3_\Delta$	C_2-0	10	8	–	3	
		3_L	C_2-1	12	6*	4*	0	
			C_2-1	8*	4*	8*	4*	
			F-1	8*	4*	4*	0	
		3_V	C_2-2	6*	3*	6*	3*	
			F-2	3*	4*	–	3*	
		$B_0+4=4_X$	R-0	3	2	–	0	
		4_T	C_2-0	4	2	4	2	
		4_U	R-1	2*	2*	2*	2*	
		$B_0+5=5$	R-0	1	1	–	1	
		Total	20	322	182	90	36	(630)

[a] Minimal obligatory shell shown for starting material; cf. eqn. (5).

[b] Number of combinations of heteroatoms (v=1 (H), 2 (O), 3 (N)); the asterisk * implies σ-transfer of carbon.

[c] The C_4Z_2 atom combinations have Y=C in the three-carbon cases (1+2) considered synthetically as an extraneous, "reagent" carbon; in the two-carbon (1+1) constructions, X or Y=C as noted in C_3Z_3 and X=Y=C in C_4Z_2, referred to eqn. (5).

[d] Zero sums are listed for cases that require cleavage of the C—C σ-bond between X and Y.

These three categories of synthetic or practical importance constitute the basis for Table 8, a more useful breakdown of the possible construction reactions. Each of the seven combinations of synthon skeleton sizes above further delimit equation (5) with more carbons and minimal obligatory shells (B_0), as illustrated in the third column of Table 8. The increased shells above B_0 are labeled as B_0+1, B_0+2, *etc.*, progressing by addition of one more shell bond each time at the positions indicated by dotted bonds, in Table 8[43]. In some cases the lower symmetry allows more than one shell of the same description, as in the 3-carbon case of $B_0+1=2_M$ in which two 2_M shells are possible when the obligatory bond between the upper carbons is a necessary part of the shell. One should observe that in $C_4(1+3)$ construction the two heteroatoms are necessarily *ortho* and a π-bond is created between them in the construction pericyclic, whereas they are also *ortho* in $C_4(2+2)$ but the bond between them (σ or π) is broken in the reaction. In $C_3(1+2)/C_3Z_3$ there are three vicinal heteroatoms while in $C_2(1+1)/C_2Z_4$ there are four.

A summary of the numbers of combinations of construction reactions by mode and σ-transfer of carbon is presented in Table 9, where it will be seen that all fragmentations (and cycloaddition-fragmentations) require σ-transfers of carbon[44]. Because of the limits on the general reaction imposed

by defining two atoms as carbons unbonded in equation (5), the total numbers, while still considerable, are lower than those in Tables 1 and 2. While not strictly comparable, since Table 1 does not incorporate C_2Z_4 and Table 2 does not include B=1 shells with σ-transfers of H, the total of 911 construction reactions in this summary (Table 9) represents a substantial reduction from the 1670 reactions in Tables 1 and 2 (or over 2000 if the noted omissions were included). If the modes C_2, F, and R are regarded as the only generally realistic ones there are 122 reactions in this summary with no σ-transfer of carbon and 145 with such σ-transfer, for a total of 267 construction reactions on a six-atom frame. It seems likely that a number of these represent viable chemical reactions which are presently unknown.

Table 9. Summary of six-center pericyclic constructions by mode.

Product span and synthon skeletons			Shells	Mode [a] $k=3$ [b] CF_3 C_3		$k=2$ [b] CF_2 C_2		$k=1$ [b] F	R	Totals σ/C*	+ other	=Σ
C_6	6	(C_6)	2						1*+1	1*	1	2
C_5	1+4	(C_5Z)	4				3*+2		2*+1	5*	3	8
	2+3		4				5		3	0	8	8
C_4	1+3	(C_4Z_2)	8			9*	6*+10	4*	2*+3	21*	13	34
	2+2		6		9		8		4	0	21	21
C_3	1+2	(C_3Z_3)	16	27*	12*+26	30*	10*+24	8*	2*+5	40*	24	64
		(C_4Z_2)	16	9*	6*+10	12*	7*+11	4*	2*+3	89*	55	144
C_2	1+1	(C_2Z_4)	20	120*	24*+31	90*	14*+16	21*	2*+4	271*	51	322
		(C_3Z_3)	20	81*	24*+20	83*	21*+16	20*	4*+3	233*	39	272
		(C_4Z_2)	20	6*	6*+3	6*	7*+2	3*	2*+1	30*	6	36
				243*	72*+99	230*	68*+94	60*	17*+28	690*	221	911

[a] Numbers of combinations are separated into those with no σ-transfer of carbon and those which require σ-transfer of carbon; the latter are flagged with asterisks.
[b] Reaction modes subdivided by number of components, k, in the starting material.

The same organization can be applied to the pentagonal frame although some new complexities appear. The greatest of these lies in the lower symmetry whereby a single reaction between two species does not fully characterize a shell; there are instead the ten α and β electron forms (Fig. 1). Hence for construction, the definition analogous to equation (5) can be handled in two equivalent ways. In one of these a single α/β pair is chosen for reference, *e.g.*, $\alpha_1 \rightleftharpoons \beta_1$, and the three non-equivalent positions for the construction pair of adjacent carbons (relative to the symmetry line) are written with an appropriate pair of interconverting structures. In the other approach, which we adopt here, the construction pair of adjacent carbons is kept constant, symmetrically placed across the vertical symmetry line, and the six symmetrically non-equivalent electron forms of Figure 1 are allowed to interconvert with respect to those carbons. Shown in Figure 2 this five-reaction set is the equivalent of equation (5) for the six-atom series above; there are three starting materials for construction (circled) and three products (the set for cleavages is the same with the reaction arrows reversed). It may be noted here that the sixth conversion $\alpha_3 \rightarrow \alpha'_3$, is not a construction on this definition.

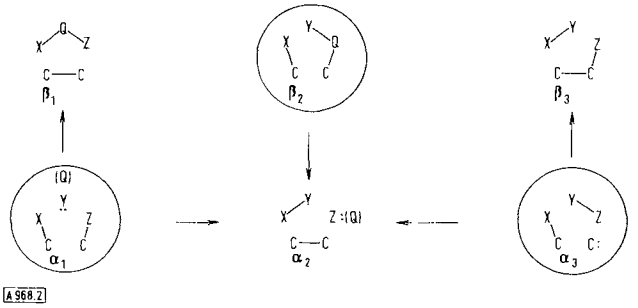


Fig. 2. Five-center electron forms in construction (starting materials are circled).

The valency changes in the five-atom set represent another variable not present in the six-atom series. In the construction

Table 10. Five-center shells and reaction modes for construction.

Shells [a]	B=1	B=2v	B=2s	B=3v	B=3s	B=4
(a)	C C	C C	C C	C C	C C	C C
(b)	C C	C C	C C			
(c)	C C	C C	C C	C C	C C	
(d)	C C					

[a] Shells below the line [(c), (d)] are symmetry duplicates if the electron-form has a vertical symmetry element (*i.e.*, in α_1 and β_1).

Shell		Electron form $\alpha_1\beta_1$	$\alpha_1\alpha_2$	$\beta_2\alpha_2$	$\alpha_3\alpha_2$	$\alpha_3\beta_3$
B=0		CF_3-4*	CF_3-3*	CF_2-4*	CF_3-3*	CF_3-4*
B=1	(a)	C_3-2*	CF_3-1*	CF_2-2*	CF_3-1	C_3-2
	(b)	CF_2-3*	CF_2-2*	F-2*	CF_2-1*	CF_2-2*
	(c)	—	CF_2-3*	CF_2-3*	CF_2-2*	C_3-2*
	(d)	—	CF_3-2*	CF_2-3*	CF_2-3*	CF_2-3*
B=2v	(a)	C_2-2*	CF_2-1*	F-1*	CF_2-0	C_2-1
	(b)	F-2*	F-2*	F-2*	CF_2-1*	C_2-1*
	(c)	—	C_2-2*	C_2-2*	C_2-2*	C_2-2*
B=2s	(a)	C_3-0	C_3-0	C_2-1	C_2-1	C_2-1
	(b)	C_2-1*	C_2-1*	C_2-1*	C_3-0	C_3-0
	(c)	—	CF_2-1*	F-1*	F-1*	F-1*
B=3v	(a)	R-1*	R-1*	R-1*	C_2-0	C_2-0
	(c)	—	R-1*	R-1*	R-1*	R-1*
B=3s	(a)	C_2-0	C_2-0	C_2-0	C_2-0	C_2-0
	(c)	—	C_2-0	R-0	R-0	R-0
B=4		R-0	R-0	R-0	R-0	R-0

* Requires σ-transfer of carbon.

from starting material α_1 there are two possible routes but the $\alpha_1 \rightarrow \beta_1$ reaction will only occur if atom Y = Q, capable of valency change $\Delta v = +1$. The comparable choice of two routes starting with α_3 will similarly depend on a valency change ($\Delta v = +1$) but the atom "Q" is now carbon; hence the $\alpha_3 \rightarrow \beta_3$ conversion requires C: to be a carbene[45] whereas for $\alpha_3 \rightarrow \alpha_2$ there is no carbon valency change and C: is a carbanion. In the $\beta_2 \rightarrow \alpha_2$ construction the atom Z = Q undergoes the reverse valency change, $\Delta v = -1$; should Q = C the product must be a carbene.

With respect to the three synthetically important distinctions applied above, the six reaction modes (CF_3, C_3, CF_2, C_2, F, R) are the same but their relation to the possible shells is more complex. The placement of each shell with respect to the two fixed carbons defining construction allows sixteen variations (including B = 0) in general, or only ten if the electron form has the same vertical symmetry element as the two placed construction carbons, *i.e.*, α_1 and β_1; these shells are detailed in Table 10 with their characteristic reaction modes set out below. The number of σ-transferred atoms is included

Table 11. Enumeration of five-center pericyclic reactions for construction.

Product Span	Half-spans	Shell	Reaction Mode and Atom Combinations				
			$\alpha_1 \rightarrow \beta_1$	$\alpha_1 \rightarrow \alpha_2$	$\beta_2 \rightarrow \alpha_2$	(carbanion) $\alpha_3 \rightarrow \alpha_2$	(carbene) $\alpha_3 \rightarrow \beta_3$
C_5	(5)	$B_0 = 4$				R-0(1)	R-0(1)
	1+4	$B_0 = 3_v$				C_2-0(1)	C_2-0(1)
	2+3	$B_0 = 3_s$			C_2-0(1)*	C_2-0(1)	C_2-0(1)
C_4	1+3	$B_0 = 2_v$	C_2-2(3) [a]	CF_2-1(3)	C_2-2(3)*	C_2-2(3)	C_2-2(3)
					F-1(Q_1)	CF_2-0(3)	C_2-1(3) [b]
(C_4Z)		$B_0 + 1 = 3_v$	R-1(2) [a]	R-1(2)	R-1(Q_2)	R-1(2)	R-1(2)
					R-1(2)*	C_2-0(2)	C_2-0(2)
		3_s	C_2-0(2) [a]	C_2-0(2)	C_2-0(2)*	C_2-0(2)	C_2-0(2)
					R-1(Q_2)	R-0(2)	R-0(2)
(α_1)		$B_0 + 2 = 4$	R-0(1) [a]		R-0(1)*	R-0(1)	R-0(2)
					R-0(Q_3)		
(C_4Z)	2+2	$B_0 = 2_s$	C_3-0(Q_1)	C_3-0(2)	C_2-1(3)*	C_2-1(3) [b]	C_2-1(3) [b]
		$B_0 + 1 = 3_s$	C_2-0(Q_2)	C_2-0(2)	C_2-0(3)*	C_2-0(2)	C_2-0(2)
					R-0(2)*	R-0(2)	R-0(2)
(α_1)		$B_0 + 2 = 4$	R-0(Q_3)		R-0(1)*	R-0(1)	R-0(1)
C_3	1+2	$B_0 = 1$	C_3-2(3Q_1)	CF_3-2(6)	CF_3-3(9)*	CF_2-3(9)	CF_2-3(9)
				CF_3-1(6)	CF_2-2(3Q_1)	CF_3-1(9) [b]	C_3-2(9) [b]
(C_3Z_2)		$B_0 + 1 = 2_v$	C_2-2(3Q_2)	CF_2-1(6)	C_2-2(6)*	C_2-2(6)	C_2-2(6)
					F-1(2Q_1)	CF_2-0(6)	C_2-1(6) [b]
		2_s	C_3-0(2Q_1)	C_3-0(8)	C_2-1(6)*	C_2-1(12) [b]	C_2-1(12) [b]
			C_2-1(2Q_2)	CF_2-1(8)	C_2-1(5Q_2) [b]	F-1(4)	F-1(4)
				C_2-1(4)	F-1(4)*	C_3-0(4)	C_3-0(4)
(α_1)		$B_0 + 2 = 3_v$	R-1(2Q_3)	R-1(2)	R-1(2)*	R-1(2)	R-1(2)
					R-1(Q_2)	C_2-0(2)	C_2-0(2)
		3_s	C_2-0(3Q_2)	C_2-0(12)	R-0(2)*	R-0(6)	R-0(6)
					C_2-0(2Q_3)	C_2-0(2)	C_2-0(6)
					C_2-0(4)*		
					R-0(2Q_2)		
		$B_0 + 3 = 4$	R-0(Q_3)		R-0(1)*	R-0(1)	R-0(2)
					R-0(Q_3)		
C_2	1+1	$B_0 = 0$	CF_3-4(6) [a] (6Q_1)	CF_3-3(6)(12)	CF_2-4(3Q_1)(9Q_1)	CF_3-3(9)(27)	CF_3-4(9)(27)
		$B_0 + 1 = 1$	C_3-2(6) [a] (6Q_1)	CF_3-1(6)(12)	CF_2-2(2Q_1)(6Q_1)	CF_3-1(6)(18) [b]	C_3-2(6)(18) [b]
			CF_2-3(6) [a] (6Q_2)	CF_2-2(6)(12)	CF_2-3(6Q_2)(15Q_2)	CF_2-3(6)(18)	CF_2-3(6)(18)
				CF_2-3(6)(12)	F-2(2Q_1)(4Q_1)	CF_2-1(6)(12)	CF_2-2(6)(12)
				CF_3-2(6)(12)		CF_3-2(6)(12)	C_3-2(6)(12)
(α_1)		$B_0 + 2 = 2_v$	C_2-2(3) [a] (3Q_2)	CF_2-1(3)(6)	F-1(Q_1)(2Q_1)	CF_2-0(3)(6)	C_2-1(3)(6) [b]
(C_3Z_2)			F-2(3) [a] (3Q_3)		F-2(2Q_2)(2Q_2)	C_2-2(3)(6)	C_2-2(3)(6)
or				F-2(3)(3)	C_2-2(3Q_3)(6Q_3)	CF_2-1(4)(4)	C_2-1(4)(4)
(C_2Z_3)		$B_0 + 2 = 2_s$	C_3-0(3) [a] (3Q_1)	C_3-0(3)(6)	C_2-1(2Q_2)(6Q_2) [b]	C_2-1(4)(12) [b]	C_2-1(4)(12) [b]
			C_2-1(4) [a] (4Q_2)	C_2-1(4)(8)	F-1(2Q_2)(4Q_2)	C_3-0(4)(8)	C_3-0(4)(8)
				CF_2-1(4)(8)	C_2-1(2Q_2)(4Q_2)	F-1(4)(8)	F-1(4)(8)
		$B_0 + 3 = 3_v$	R-1(2) [a] (2Q_3)		R-1(Q_2)(Q_2)	C_2-0(2)(2)	C_2-0(2)(2)
					R-1(2Q_3)(2Q_3)	R-1(2)(2)	R-1(2)(2)
		$B_0 + 3 = 3_s$	C_2-0(2) [a] (2Q_2)		C_2-0(2Q_3)(4Q_3)	C_2-0(2)(4)	C_2-0(2)(4)
					R-0(Q_2)(2Q_2)	R-0(2)(4)	R-0(2)(4)
		$B_0 + 4 = 4$	R-0(1) [a] (Q_3)		R-0(Q_3)(Q_3)	R-0(1)(1)	R-0(1)(1)

Notes: Atom combinations are shown in parenthesis; Q_1, Q_2, Q_3 represent the numbers of possible valency-change atoms or groups of Table 5, with $V = 1 \rightleftarrows 2$, $2 \rightleftarrows 3$, $3 \rightleftarrows 4$, respectively. The two parentheses in $C_2(1+1)$ represent C_3Z_2 (with Y = C) first and C_2Z_3 second.

* Carbene products.

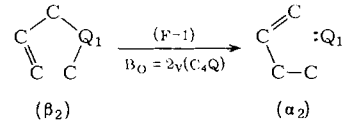
[a] Carbene starting materials in $\alpha_1 \rightarrow \beta_1$ with atom Y = C.

[b] No σ-transfer of carbon; all other σ-transfer involve carbon (see Table 10).

in Table 10 following the code format used in the six-atom Table 7. Here another variable also arises in the change from a σ-bond to an unshared pair, —A⇌:A, not found in the six-atom cases. This change is not included as a σ-transfer since the stereoelectronic demands here must be substantially less than in a true σ-transfer and so the practicality of such reactions is of a higher order. In virtually all cases in which the shell requires a σ-transfer, one (or both) of the construction carbons must be σ-transferred and these are flagged in Table 10. The only exceptions are B=1(a), 2_V(a), and 2_S(a) for conversions starting with the α_3 form and B=2_S(a) in the $\beta_2 \rightleftharpoons \alpha_2$ conversion, where it is atom Y that is σ-transferred. The distinctions among combinations of synthon skeleton sizes are fewer here, only the six listed above for C_2—C_5 but the greater asymmetry of the five-ring set requires that both (1+2) and (2+1) be enumerated for C_3 and both (1+3) and (3+1) for C_4, *i.e.*, placing the carbon-skeleton moieties on both the left and right side in the forms of Figure 2. The five-atom cases, however, do allow the variation of using an extraneous, or "reagent" carbon only at site Y and only in the C_2(1+1) examples, which may thus be either C_2Z_3 or C_3Z_2 atom combinations.

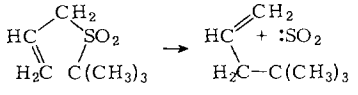
A complete tabulation of these separate combinations is assembled as Table 11, comparable with Table 8. As before no C—C σ-bond cleavages are allowed, carbene products and carbene starting materials (other than α_3) are flagged, the latter appearing in $\alpha_1 \rightarrow \beta_1$ when atom Y=C. Blank positions indicate either no possible reaction or one duplicated in another column, usually $\alpha_1 \rightarrow \alpha_2$ equivalent to $\alpha_3 \rightarrow \alpha_2$ by anion resonance. In the enumeration, hydride and halide ($H:^{\ominus}$ and $X:^{\ominus}$) were disallowed in a starting material. Table 11 is further summarized as before in Table 12, sorted by reaction mode and σ-transfers of carbon.

The full tabulations in Tables 8 and 11 are extensive and complicated at first sight. This is not unexpected in view of the many possible combinations of pericyclic reactions. However, their breakdown by several different useful distinctions creates their value, for it is possible to find reactions incorporating several specified features and the groups so defined rarely number over a dozen and so are easily examined. The definitions allow formulation of the specific reactions in the group for examination of new useful reactions. Hence the tables, though complex, serve as a useful source base for the invention of new constructions. As an example, examine the five-atom pericyclic reaction uniting a one- and a three-carbon moiety (*i.e.* C_4(1+3)) by the $\beta_2 \rightarrow \alpha_2$ route such that all atoms are linked prior to reaction, which requires $k=1$ or F and R reaction modes. The smallest shell is then $B_0=2_V$ as a fragmentation with one σ-transfer of carbon (F-1); larger shells ($B_0+1=3_V$ or 3_S; $B_0+2=4$) are rearrangements with a σ-transfer (R-1) for B=3 and none (R-0) for B=4[46]. The basic case may be written as in equation (6) and the number of atom-combinations is only the number of possible groups Q_1.



(6)

We tried the specific example (6a) and found a smooth thermal conversion at 300 °C[47]. The starting material is easily


(6a)

created by bubbling SO_2 into *tert*-butyllithium solution and alkylating the resultant *tert*-butyl sulfinate with allyl bromide. The conjugated isomer, *via* potassium carbonate-catalyzed isomerization, is incapable of pericyclic fragmentation and indeed is stable at 300 °C and decomposes into a number of products at higher temperatures. The reaction thus shows considerable potential for construction, especially as it is capable of creating a quaternary carbon in the product, even though the reaction requires a σ-transfer of one construction carbon.

Table 12. Summary of five-center pericyclic constructions by mode.

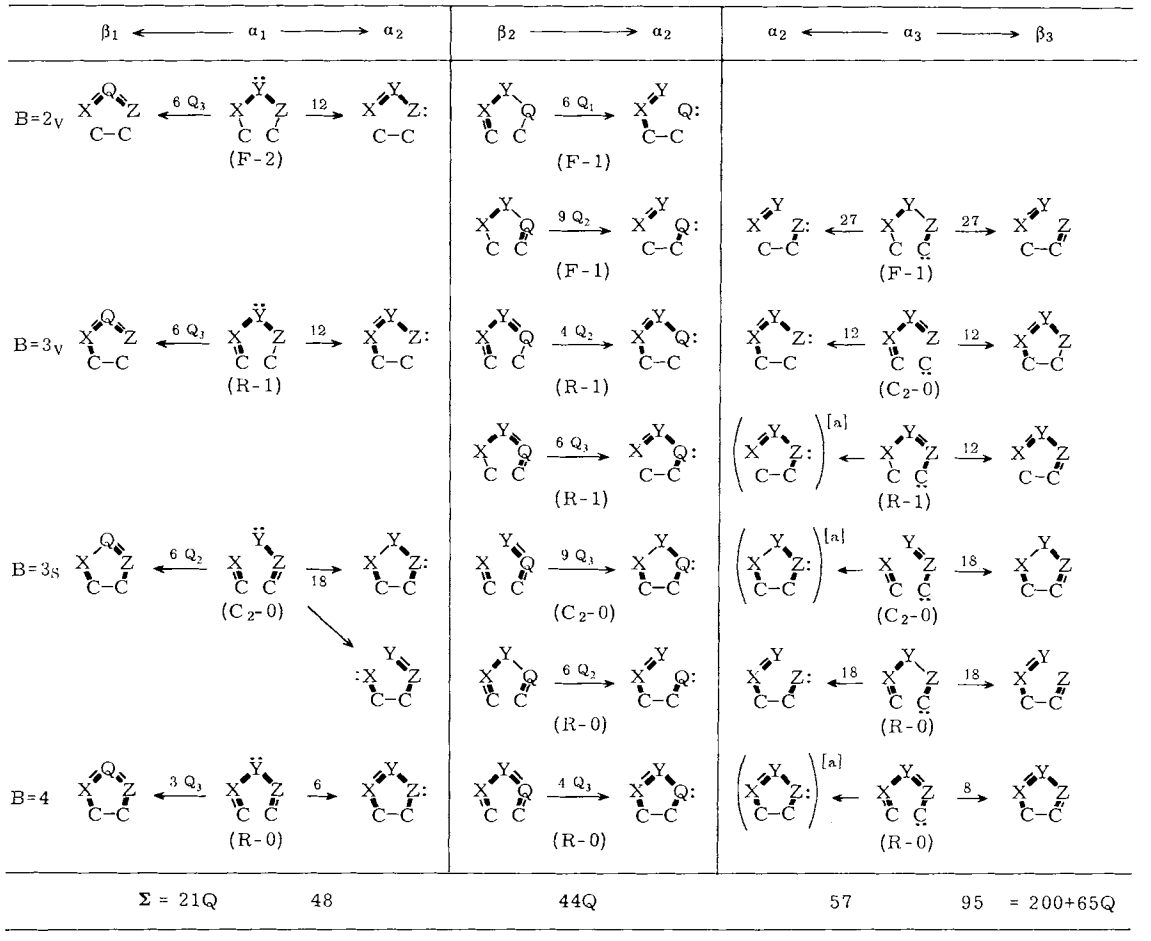
Product span and synthon skeletons			Shells	Mode [a] $k=3$ [c] CF_3	C_3	$k=2$ [c] CF_2	C_2	$k=1$ [c] F	R	σ/C	Totals + Others	=Σ
C_5	5	(C_5)	1						2	0	2	2
	1+4		1				2			0	2	2
	2+3		1				2			0	2	2
C_4	1+3	(C_4Z)	4			3	15		8+Q		26+Q	
			(σ) [b]			3	9	Q	8+2Q	20+3Q		46+4Q
	2+2		3		2+Q		12+Q		6+Q	0	20+3Q	20+3Q
C_3	1+2	(C_3Z_2)	8	9	25+2Q	6	54+10Q		15+4Q		109+16Q	
			(σ) [b]	12	3Q	32+3Q	16+5Q	8+2Q	6+3Q	74+16Q		183+32Q
C_2	1+1	(C_3Z_2)	16	6	20		21+4Q		7+2Q		54+6Q	
			(σ) [b]	48	12	56+11Q	21+5Q	14+7Q	6+3Q	157+26Q		211+32Q
		(C_2Z_3)	16	18	40+3Q		42+12Q		10+4Q		110+19Q	
			(σ) [b]	102+6Q	12+6Q	108+36Q	24+17Q	19+15Q	4+5Q	269+85Q		379+104Q
		Total		33	87+6Q	9	148+27Q		46+12Q		325+45Q	
			(σ) [b]	162+6Q	24+9Q	199+50Q	70+27Q	41+25Q	24+13Q	520+130Q		845+175Q

[a] Numbers of combinations shown include Q, a value for the number of valency-change groups possible.
[b] σ-transfer of carbon required.
[c] Reaction modes subdivided by number (k) of starting components.

Assuming from Table 11 and 12 that the only practical reactions are in C_2, F, and R modes with no more than one σ-transfer of carbon in F and R and none in C_2, we may collect the possible examples into the more graphic presentation of Scheme 8[48].

adding a shell bond between the carbons in equation (5), or in the five-atom set in Figure 2. Focusing on the immediate environment of the pair of carbons allows a subdivision into three successive partial shells, B_0, as shown in Scheme 9, illustrated as six-atom reactions but understood to include

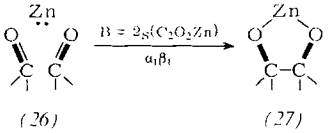
Scheme 8. Selected five-center construction reactions.



[a] These products also appear in other reactions and are not counted here.

The 25 transformations generalized in the chart represent 200 + 65Q combinations of atoms (including carbon), depending on the number of viable Q groups (Table 5). Two reactions here are not obligatory pericyclics in an α→α′ conversion since the initial and final atoms bearing unshared pairs are not shell-bonded, as noted above. They are included nevertheless, *viz.*, $B=3_S(\alpha_1\rightarrow\alpha'_2)$ and $B=3_V(\alpha_3\rightarrow\alpha_2)$. The familiar 1,3-dipolar addition[27] (C_2—O) as a construction reaction is seen in $B=3_S(\alpha_1\rightarrow\alpha_2$, or its resonance duplicate, $\alpha_3\rightarrow\alpha_2)$. That some constructions may, however, be valid in lower shells is implied in the pinacol reduction (*(26)→(27)*) which may be formulated as $B=2_S(C_2O_2Zn/\alpha_1\beta_1)$, as a C_3—O cycloaddition mode and hence not included in Scheme 8, although it is of course included in the more general Table 11.

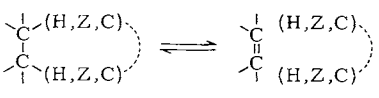
Elimination-addition equilibria can be formulated in a completely analogous manner to construction (cleavage) simply by



five-atom examples by contraction of the undefined, dotted right-hand region of each set. There are a total of 15 variations possible, described roughly to relate them to commonly understood families of reactions. A number of these variations are trivial, such as the ketone-enol equilibria, β-eliminations, and conjugate additions, many of which need not be pericyclic. A number of others involve construction or cleavage and so would more reasonably be considered under the previous discussion of construction reactions. Such a procedure implies more central importance given to making and breaking the C—C σ-bond. However, decarboxylations may more usefully be seen as eliminations and are noted in Scheme 9; since the carboxyl, however, occupies all the remaining atom positions in the six-atom set, there are only a few variations possible, all well known. Finally, the allylic rearrangements and double-bond isomerizations may more clearly be seen as refunctionalizations of allylic (three-carbon) systems and are treated below. Thus the synthetically most important groups may be reduced to these three: $B_0=1/HZ$ and ZZ; and $B_0=2_O/ZZ$.

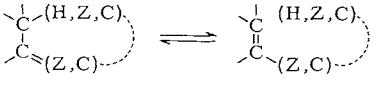
This important set of eliminations/additions is enumerated for the six-atom frame in Table 13 in a manner analogous to that for constructions in Table 8. The total number of

Scheme 9. General types of pericyclic addition/elimination reactions.



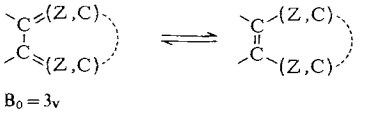
$B_0 = 1$

HH	Dehydrogenation/hydrogenation
HZ	Acetate (and Chugaev) pyrolyses
HC	Cleavage/construction
ZZ	Reductive elimination/oxidative addition
ZC	Cleavage/construction (decarboxylation)
CC	Double cleavage/construction



$B_0 = 2_O(2_V)$ [a]

HZ	Enolization/ketonization
HC	Double-bond isomerization
ZZ	Reductive elimination/oxidative addition
ZC	Allylic rearrangements (β-elimination/conjugate addition of heteroatoms)
CZ	Cleavage/construction (decarboxylation)
CC	Cleavage/construction (decarboxylation)



$B_0 = 3_V$

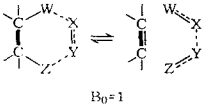
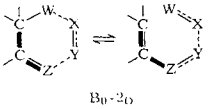
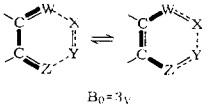
ZZ	α-Diketone reduction/enediol oxidation
ZC	Unsaturated ketone reduction (or conjugate addition)
CC	1,4-Addition to dienes/1,4-elimination

[a] Labeled for analogous five-center system.

possible reactions is listed followed by an enumeration of the HZ and ZZ cases from Scheme 9 ($W \neq C \neq Z$); these are broken down into cases with no carbons at X,Y(C_2Z_4), one "reagent" carbon at those sites (C_3Z_3) or two (C_4Z_2). Reactions taken as "viable" and separatedly totaled are the R, F, and C_2 modes.

three categories with one, two, and three carbon bonds to heteroatoms, respectively (these are the functional families, Z = 1, 2, and 3, in Ref. [39]). The three types are illustrated on the six-atom frame, but the five-atom set is easily examined, at least in the first two, by following the analysis for constructions (cf. p. 63) and substituting heteroatom B for one construc-

Table 13. Enumeration of six-center pericyclic addition/elimination reactions.

	Shells	Reaction direction Elim. ⟶	Addn. ⟵	All	Atom combinations C_2Z_4	C_3Z_3	C_4Z_2	Σ
 $B_0 = 1$	$B_0 = 1$	$(CF_2\text{-}4$	$CF_3\text{-}4)$	136	45	27	6	78
	$B_0 + 1 = 2_M$	F-2	$(C_3\text{-}2)$	144	36	30	6	72
	2_P	$(CF_2\text{-}2$	$CF_2\text{-}2)$	78	21	18	6	45
	$B_0 + 2 = 3_\Delta$	F-0	$C_3\text{-}0$	45	10	8	3	21
	3_L	F-1	$C_2\text{-}1$	72	12	18	6	36
	$B_0 + 3 = 4_T$	F-0	$C_2\text{-}0$	21	3	4	3	10
		Totals		496	127	105	30	362
		"Viable"		282	61	60	18	139
 $B_0 = 2_O$	$B_0 = 2_O$	$(CF_2\text{-}3$	$CF_2\text{-}3)$	192	54	36	6	96
	$B_0 + 1 = 3_L$	F-1	$C_2\text{-}1$	108	24	20	4	48
	3_L	$C_2\text{-}1$	F-1	108	24	24	6	54
	3_V	F-2	$(C_2\text{-}2)$	96	18	15	3	36
	$B_0 + 2 = 4_X$	R-0	R-0	54	8	12	4	24
	4_T	F-0	$C_2\text{-}0$	54	8	8	2	18
	4_U	R-1	R-1	48	6	9	3	18
	$B_0 + 3 = 5$	R-0	R-0	24	2	4	2	8
		Totals		684	144	128	30	302
		"Viable"		492	90	92	24	206
 $B_0 = 3_V$	$B_0 = 3_V$	$(C_2\text{-}2)$	F-2	78	21	12	3	36
	$B_0 + 1 = 4_T$	$C_2\text{-}0$	F-0	45	10	8	3	21
	4_U	R-1	R-1	72	12	10	2	24
	$B_0 + 2 = 5$	R-0	R-0	36	4	6	2	12
	5	R-0	R-0	21	3	2	1	6
		Totals		252	50	38	11	99

A comparable breakdown of eliminations and additions on the five-atom frame, analogous to the analysis in Table 13, can be made in a similar fashion but is of course considerably more complex, as it is for constructions. The Corey carbene procedure[49] is an example of elimination of the ZZ sort from the first group [($B_0 = 1$) in Scheme 9] on a five-atom frame, annotated as $B_0 + 2 = 3_S(C_3O_2/\alpha_1\beta_1)$.

Refunctionalization reactions can also be analyzed in a comparable way. Again, as shown in Table 14, a focus on the different reaction types with respect to the functionality of the involved carbon undergoing refunctionalization yields

tion carbon. In all the substitution group the central carbon is necessarily σ-transferred (Table 14), and few examples are presently known. In each case the various possible shells represent all combinations on filling the dotted shell bonds, which are missing in the basic parent definition of B_0. However, in the substitutions it was also assumed that a shell bond must always exist between A—X since otherwise a cycloaddition to a C—H or C—Z σ bond is implied; this more stringently limits the possible shells. In Table 14 only "viable" reaction modes (R, F, C_2) were listed. In some cases the shells allow σ-transfer of B = H and so the reactions are poten-

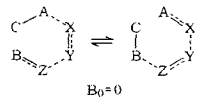
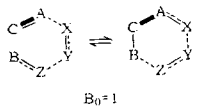
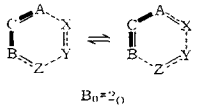
tial reductions. The Meerwein-Ponndorf-Verley reduction (and probably the analogous Cannizzaro and Leuckart reductions) is a likely example of $B_0+2=3_L(C_2O_2AlH)_M$; F-1, in the second group. In general, despite their considerable number, these refunctionalizations appear to be of little potential value and examples presently known are rare.

Examining the refunctionalizations further in terms of synthon carbon-skeleton size, we may follow the same analysis as that used for constructions above and examine re-ordering of functionality on C_2, C_3, and C_4 skeletons, in which the skeletal carbons are part of the pericyclic atom set. Thus we will successively replace A, then A and X, and finally A, X, and Y with carbons and link all carbons with shell bonds. In this way we see that the C_2 and C_4 skeletons become, respectively, olefins and dienes and their refunctionalizations are simply the addition/elimination reactions of Table 13. With the C_3 skeleton we may separately analyze allylic refunctionalizations as shown in Table 15, again for the six-atom cases. The five-atom cases are found in Table 11 for $C_4(1+3)$ by replacing the C_1 synthon carbon by heteroatoms.

6. Energy Considerations

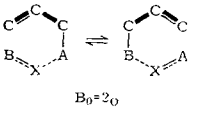
Most of these pericyclic reactions have not been realized experimentally, but a great many could be of practical importance. The previous sections provide protocols for selecting or devising pericyclic reactions to fit specific interconversion requirements. There remains the question of the availability of means for manipulating the reactions to improve the probability of their success. The reactions are equilibria and the thermodynamic energy preference of any given reaction is amenable to calculation from bond energies (Table 3), but the values available are taken from unrelated experimental situations and are often highly dependent on molecular environment[50]. The study of pericyclic equilibria themselves could provide more meaningful bond energy data under nonpolar

Table 14. General types of pericyclic refunctionalization reactions.

	Substitution	Reaction direction ⟶	Reaction direction ⟵	Atom combinations B=N, O	Atom combinations B=H	Σ
 $B_0=0$	$B_0+2=2_M$	F-2	F-2	108	54	162
	$B_0+3=3_V$	F-2	F-2	48	24	72
	3_L	F-1	C_2-1	72	0	72
	$B_0+4=4_U$	R-1	R-1	32	0	32
			Totals	260	78	338
	Ketalization					
 $B_0=1$	$B_0+2=3_L$	F-1	C_2-1	54	27	81
	3_L	C_2-1	F-1	36	0	36
	3_L	C_2-1	F-1	72	36	108
	3_L	C_2-1	F-1	96	0	96
	$B_0+3=4_X$	R-0	R-0	36	0	36
	4_T	C_2-0	F-0	48	0	48
	4_T	C_2-0	F-0	36	0	36
	4_U	R-1	R-1	24	12	36
	$B_0+4=5$	R-0	R-0	16	0	16
			Totals	418	75	493
	Ester Refunctionalization					
 $B_0=2_O$	$B_0+1=3_L$	F-1	C_2-1	108		
	3_V	F-2	(C_2-2)	96		
	$B_0+2=4_X$	R-0	R-0	72		
	4_T	C_2-0	F-0	54		
	4_U	R-1	R-1	48		
	4_U	R-1	R-1	36		
	$B_0+3=5$	R-0	R-0	24		
	5	R-0	R-0	18		
			Total	456		

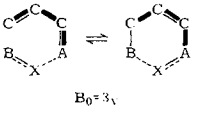
Note: A and B are heteroatoms (or H) and X, Y, and Z are H, O, N or C.

Table 15. Allylic refunctionalizations.



$B_0=2_O$

$B_0=2_O$	(CF_2-3	CF_2-3)	24
$B_0+1=3_L$	F-1	C_2-1	18
$B_0+2=4_X$	R-0	R-0	6
		Total	48



$B_0=3_V$

$B_0=3_V$	(C_2-2)	F-2	24
$B_0+1=4_T$	C_2-0	F-0	12
4_U	R-1	R-1	18
$B_0+2=5$	R-0	R-0	4
		Total	58

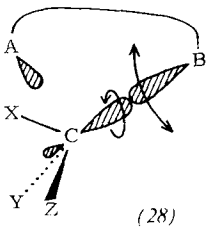
conditions. Unfavorable equilibria may often be reversed in practice by removal of the higher-energy reaction partner, as realized and discussed by *Evans et al.*[51] in their manipulation of a pentagonal $B=3_S(C_3SO/\alpha_3\alpha'_3)_V$.

The reactions are also self-contained and thermal, so that the key experimental feature is the required threshold temperature and this is rarely amenable to alteration by external influences (solvents, catalysis, *etc.*). This temperature directly reflects the activation energy and is very widely different among known cases. Many presently unknown pericyclic reactions may have been overlooked simply because relatively simple and well-known potential substrates have not been deliberately heated above 300 °C. Many others which do not appear to proceed may be pre-empted by competitive reactions of lower activation energy, perhaps involving catalytic acid-base initiation *via* Z—H and Z: groupings activated at elevated temperature. We have at present only very primitive approaches to any semiquantitative assessment of activation energy and resonance stabilization of the transition state, or of the position of the transition state on the reaction coordinate. We lack in most instances even qualitative evaluation of the effects of varying atom combinations or substituents on the pericycle, or of the relative importance of stereoelectronic demands.

There are, however, a few qualitative considerations about the activation energy—and thus the required threshold temperature—which may be useful in the selection and design of reactions. The high degree of molecular organization required to approach a pericyclic transition reflects a generally high entropy of reaction as a factor in the activation energy. At the grossest level this implies that preassembly of the involved atoms is to be preferred, *i.e.*, rearrangements (R) and fragmentations (F) over cycloadditions (C) in reaction mode. This is qualitatively borne out by the generally higher temperatures required for cycloadditions like the Diels-Alder reaction than for known fragmentations and reorganizations. Furthermore, the stereoelectronic requirements of the reaction may be assessed by application of the Woodward-Hoffmann rules to examine in models the required geometry for maximum overlap of the correct orbitals. This further allows an evaluation of the steric hindrance of non-bonded groups in the transition state. The valuable generalization of a preference for chair conformation in the Claisen rearrangement[14] can be used to evaluate the steric difficulties of axial substituents in the transition.

The involvement of π bonds in the pericycle is probably preferred over that of σ bonds, not only because of their lower energy but also because the more accessible π cloud is more mobile or polarizable and so more adapted to stabilizing overlap early on the reaction coordinate. Conversely, σ-transfer of carbon is unfavorable not only because of inaccessibility of the tight σ bond for overlap but also because of the higher entropy implicit in correct rotation of the carbon and its substituents on the two axes (cf. *(28)*).

The effects of substituents for resonance stabilization of the pericycle are poorly understood in general. In the Diels-Alder cycloaddition the generalization concerning electron-withdrawing substituents on one component and electron-donating ones on the other[52] may have more to do with the initial association of the two components than with stabilization of the transition state and so not be useful if carried over to considerations of fragmentation or rearrangement modes.

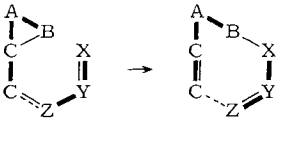


(28)

Transition state theory implies that lowering the energy of the products or raising that of the starting materials will lower the activation energy[53]. An analysis of the options for achieving this can be helpful in reaction design. In the hexagonal frame three bonds are broken and three are made. A more favored reaction will result if the former are relatively low-energy bonds, such as σ bonds between heteroatoms (N—N, N—O, *etc.*) or in strained three-membered rings (see Table 3). Similarly, if the bonds made release large amounts of energy the same effect is achieved, as in liberation of N_2 or CO_2.

Placement of such vicinal atom pairs at the proper sites in the pericycle should facilitate the reaction and this provides a basis for an analysis of equation (5), shown in Table 16, for construction and elimination reactions. In the first example, the possible combinations are listed as before for formation of a π bond (between atoms A and B) and extrusion (σ-bond breaking), as in N_2 and CO_2. The opportunities for using these favorable products are clearly more limited than the possibilities for designing the reactions enumerated in the last section. The second set of examples similarly explores the breaking of a weak σ bond, between A and B (*e.g.* the cleavage of N—N and N—O bonds; noted in the discussion of Scheme 3). A minimal shell prerequisite is taken to be the B—Y bond since without it a cycloaddition to a σ bond (with σ-transfers) is required. In selecting examples from the last section for synthesis, these further limitations can be placed on the selection if desired. Since decarboxylation implies C—C cleavage, it was omitted from the enumerations of construction reactions previously (Section 5) and such constructions are best formulated *via* Table 16.

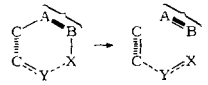
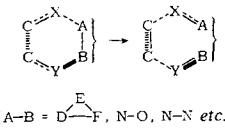
Cleavage of a three-membered ring may be utilized as part of the second set in Table 16, but there are three further options, explored in Table 17 and utilizing in part cross-bond shells. In the first set atoms A—B are not varied in the enumeration, as in Table 16, but the given A—B combinations include six kinds (C—C, C—N, N—C, N—N, O—C, O—N), thus considerably magnifying the totals. Also the obligatory shell bond B—X was chosen to eliminate cycloadditions with σ-transfers in construction; in elimination, however, this condition is not necessary and an additional 30 examples exist with no shell bond at B—X but rather a partial shell at X—Y and Y—Z (and C—C) as in equation (7), *i.e.* $B=3$ (F-1)(18) and $B=4_U$(R-1)(12).



(7)

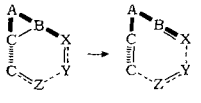
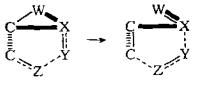
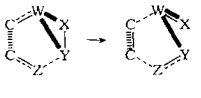
In general, since the options for utilizing three-membered ring opening to facilitate reaction are far more than those for other favorable bonds, there is a strong implication that design of pericyclic synthetic reagents incorporating such rings

Table 16. Enumeration of possibilities for lowering activation energy.

	Construction		Combinations [b]	Elimination	
1. Favorable π-bond made [a]  (A–B = CO–O, O–CO, N=N *etc.*)	$B_0 = 1$	(CF_2-4)	(16)	$B_0 = 2_M$	(F-2)
	$B_0 + 1 = 2_M$	(F-2)	9	$B_0 + 1 = 3_\Delta$	(F-0)
	2_P	(CF_2-2)	(12)	3_L	(F-1)
	$B_0 + 2 = 3_L$	(F-1)	6	$B_0 + 2 = 4_T$	(F-0)
		Total	43		
		"Viable"	15		
2. Favorable σ-bond broken [a]  (A–B = D(E)–F, N–O, N–N *etc.*)	$B_0 = 1$	(CF_2-4)	(12)	$B_0 = 2_M$	(F-2)
	$B_0 + 1 = 2_O$	(CF_2-3)	(8)	$B_0 + 1 = 3_V$	(F-2)
	2_M	(F-2)	9	3_Δ	(F-0)
	2_P	(CF_2-2)	(9)	3_L	(F-1)
	$B_0 + 2 = 3_L$	(F-1)	6	$B_0 + 2 = 4_T$	(F-0)
	3_L	(F-1)	6	4_T	(F-0)
	3_L	(C_2-1)	6	4_U	(R-1)
	$B_0 + 3 = 4_X$	(R-0)	4	$B_0 + 3 = 5$	(R-0)
		Total	60		
		"Viable"	31		

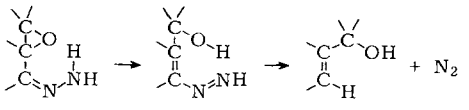
[a] Construction is without and elimination with the dashed shell bond between carbons; both yield the same numbers of atom combinations [b]. The favorable bond is bracketed between A—B.
[b] Atom combinations for atoms H, O, N, C in positions X, Y; those in parentheses represent less viable reaction modes (in construction) and are omitted from the second total ("viable").

Table 17. Enumeration of three-membered ring cleavages for facilitating reaction [a].

	Construction		Combinations [b]	Elimination	
1. 	$B_0 = 1$	(CF_2-4)	(48)	$B_0 = 2_M$	(F-2)
	$B_0 + 1 = 2_O$	(CF_2-3)	(24)	$B_0 + 1 = 3_L$	(F-1)
	2_M	(F-2)	27	3_Δ	(F-0)
	2_P	(CF_2-2)	(36)	3_L	(F-1)
	$B_0 + 2 = 3_V$	(F-2)	12	$B_0 + 2 = 4_T$	(F-0)
	3_L	(C_2-1)	18	4_X	(R-0)
	3_L	(F-1)	18	4_T	(F-0)
	$B_0 + 3 = 4_U$	(R-1)	8	$B_0 + 3 = 5$	(R-0)
		Total	191		
		"Viable"	83		
2. 	$B_0 = 1'$	(CF_2-4)	(96)	$B_0 = 2'_M$	(F-2)
	$B_0 + 1 = 2'_O$	(C_2-3)	(36)	$B_0 + 1 = 3'_L$	(R-1)
	$2'_M$	(F-2)	54	$3'_\Delta$	(F-0)
	$2'_P$	(C_2-2)	(72)	$3'_L$	(R-1)
	$B_0 + 2 = 3'_L$	(C_2-1)	27	$B_0 + 2 = 4'_X$	(R-0)
	$3'_L$	(R-1)	36	$4'_T$	(R-0)
	$3'_V$	(R-2)	18	$4'_T$	(R-0)
	$B_0 + 3 = 4'_U$	(R-1)	12	$B_0 + 3 = 5'$	(R-0)
		Total	351		
		"Viable"	147		
3. 	$B_0 = 1'$	(CF_2-4)	(72)	$B_0 = 2'_M$	(F-2)
	$B_0 + 1 = 2'_O$	(CF_2-3)	(36)	$B_0 + 1 = 3'_V$	(F-2)
	$2'_M$	(F-2)	36	$3'_\Delta$	(F-0)
	$2'_P$	(C_2-2)	(54)	$3'_L$	(R-1)
	$B_0 + 2 = 3'_L$	(R-1)	18	$B_0 + 2 = 4'_T$	(R-0)
	$3'_L$	(C_2-1)	27	$4'_U$	(R-1)
	$3'_L$	(R-1)	24	$4'_T$	(R-0)
	$B_0 + 3 = 4'_X$	(R-0)	12	$B_0 + 3 = 5'$	(R-0)
		Total	279		
		"Viable"	117		

[a] Constructions and eliminations as in Table 16. The last two sets are labeled with standard shell labels for the peripheral shells and primed to indicate a cross-bond, which changes the reaction mode in some cases.
[b] Atom combinations for H, O, N, C in positions X, Y, Z; in set I, atoms A and B are not varied.

should be especially profitable. The bond energies (Table 3) make particularly favorable the opening of epoxide with attendant carbonyl formation [Table 17, set 2 (X = C, W = O) or set 3 (X = O, W = Y = C)]. Relevant examples are illustrated in the second row of Scheme 7. The opening of epoxide may also be pericyclic in the transformation *(29)*→*(30)*[54], *i.e.*, $B = 3_V(C_2N_2OH)_O$, with a calculated $\Delta E = 5$; here the equilibrium is shifted, however, by the second reaction, losing nitrogen.



(29) *(30)*

Similar analyses for favorable bond making or breaking in pentagonal frames can be set up by defining the bonds made or broken in each of the three starting materials of Figure 2, but the analysis is predictably much more complex. It may be noted that for bonds broken, most of these are bonds to the construction carbon itself, thus excluding N—N, N—O, *etc.* combinations but offering many potential three-membered ring cleavages (with σ-transfer of carbon) for facilitated construction reactions.

Finally, the special feature of the valency change at the "Q" atoms in the pentagonal frame (α⇌β transformations) can confer a special favorability in energy considerations as this change frequently affords a strong driving force. This is especially clear in the unique high-energy carbene implicit in the $\alpha_3 \rightarrow \beta_3$ transformation, but is also illustrated in the pinacol reduction (*(26)*→*(27)*).

7. Summary and Outlook

The number of six-electron thermal pericyclic reactions possible by the expansion of the basic aromatic definition is very large. Depending on the level of discrimination in the definition of involved atoms and groups, the number is in the thousands. Any practical comprehension of the scope of so large a group of reactions requires a systematic ordering in terms of meaningful molecular features so that particular reactions fulfilling specific requirements may be selected for examination. To this end the features of synthetic utility (construction, elimination, refunctionalization, *etc.*), reaction mode (R, F, C_2, *etc.*), σ-transfer, synthon skeleton size, and energy facilitation were introduced as bases for division of the total into manageable subsets of reactions. The difference between the potential and the realized scope of the thermal pericyclic reaction is still enormous. This fact leads to the prediction of several kinds of research:

1. New pericyclic reactions can be invented to fulfill specific synthetic needs by design of appropriate molecular units which, by attachment and pericyclic reorganization, can reshape a given structure in desired ways.

2. Many transformations now understood as ionic and/or multistep processes of other kinds may, on reexamination, also possess a pericyclic path.

3. Many relatively simple compounds, normally thought of as stable, may undergo pericyclic reorganization at higher than normal temperatures. It must be appreciated that high temperature is not necessarily destructive.

Examples of all of these possibilities are considered in the present report. The next step would appear to be the construction of a thorough organized catalog of presently known pericyclic or potentially pericyclic transformations. A search for these examples in the literature has been begun and an abbreviated Appendix of known pericyclic reactions is included here. The author welcomes correspondence both on the methodology of organization for the full catalog and on specific examples, easy to overlook, from the literature.

The author wishes to express his gratitude both to members of his research group, and to Mr. Samuel Silver, at Brandeis University, and to many interested chemists in lecture audiences over the past year for stimulating discussions, relevant conceptual points, and interesting pericyclic reactions.

8. Appendix

Selected Literature Examples

The list of 130 examples selected below is a sampling, mostly from the past five years, containing all the shell types and many atom combinations. The total number of known pericyclic examples is probably several hundred. Some 720 earlier references in the extensive review of *Mathieu* and *Valls*[116] have not been included. Some references contain multiple pericyclic reactions and appear in more than one location. Asterisked examples imply cases for which the listed pericyclic mechanisms were not considered by the authors.

Reaction [a]		Mode [b]	σ-Transfer carbon	σ-Transfer other	Reaction Type Construction [c]	Elimination [d]	Addition [d]	Refunctionalization [e]	Ref.
1. Six-Center Model									
B = 0	(H_6)	CF_3	0	6	—	—	—	—	[10]
B = 1	$(C_2OXH_2)_O$	CF_2	0	4	—	HO-1	—	—	[55]
$B = 2_O$	$(C_4OH)_O$	(CF_2)	1	1	1+3	HC-2	CC-2	—	[56]
	$(C_4OX)_M$*	CF_2	2	1	1+2	—	CO-2	XO(S)	[57, 58]
	$(C_3OXM)_V$	CF_2	1	2	1+2	—	CO-2	—	[73]
$B = 2_M$	$(C_3O_2H)_{VM}$	F	0	2	—	CO-1	—	—	[59]
	$(C_2N_2OX)_{MO}$	F	1	1	—	—	—	XO(S)	[9]
	$(C_2BOXH)_O$*	F	0	2	—	HO-1	—	—	[60]
$B = 2_P$	$(C_3O_2M)_{VM}$*	(CF_2)	1	1	1+1	—	—	—	[61]
$B = 3_\Delta$	$(C_2N_3O)_{OV}$*	F	0	0	—	—	—	—	[62]
$B = 3_L$	(C_6)	(C_2)	1	0	1+3	CC-1,2	CC-2	—	[56]
	(C_5O)	(C_2)	1	0	1+2	—	CC-1,2	—	[56]
	(C_5H)	C_2	0	1	2+3	HC-2	HC-1	—	[63] [f]
		(F)	0	1	-	HC-2	HC-2	—	[64]

Reaction [a]		Mode [b]	σ-Transfer carbon	σ-Transfer other	Reaction Type: Construction [c]	Elimination [d]	Addition [d]	Refunctionalization [e]	Ref.
1. Six-Center Model (cont'd.)									
	$(C_4NH)_O$*	(C_2)	0	1	2+2	—	HC-1	—	[65]
	$(C_4O_2)_M$	(C_2)	1	0	1+2	—	CO-2	OO(S)	[66]
	$(C_4OH)_O$	(C_2)	0	1	2+2	—	HC-1	—	[67, 75]
					1+3	HC-2	CC-2	—	[68]
	$(C_4OH)_P$	F	0	1	—	HO-1	HO-2	—	[69]
	$(C_3N_3)_V$	F	1	0	1+2	—	—	—	[70]
	$(C_3O_2H)_{LM}$	F	0	1	—	HO-1	—	—	[179]
	$(C_3OSH)_L$	F	0	1	—	HO-1	—	—	[179]
	$(C_3BOX)_V$*	C_2	0	1	1+2	—	CX-1	—	[60]
	$(C_2NOSH)_P$	F	0	1	—	—	—	OH(K)	[71]
	$(CN_4H)_X$	C_2	0	1	—	—	—	NN(K)	[63]
B=3V	$(C_4XH)_O$	F	0	2	—	HC-2(XC-2)	—	—	[55]
		C_2	0	2	—	—	HC-2(XC-2)	—	[72]
	$(C_2N_2OH)_{OO}$*	F	0	2	—	—	ON-3	—	[74]
B=4X	(C_6)	R	0	0	3+3	CC-2	CC-2	—	[1, 14] [f]
	(C_5N)	R	0	0	2+3	CN-2	CN-2	—	[77, 78, 79]
		R	0	0	1+4	—	CC-2	—	[17]
	(C_5O)	R	0	0	2+3	CO-2	CC-2	—	[80, 81] [f]
	(C_5S)	R	0	0	2+3	CS-2	CC-2	—	[82, 83]
	$(C_4N_2)_O$	R	0	0	2+2	—	CN-2	—	[84]
	$(C_4NO)_O$	R	0	0	2+2	—	CN-2	—	[85]
	$(C_4NS)_M$	R	0	0	—	CS-2	CN-2	NS(A)	[86]
	$(C_4O_2)_M$	R	0	0	—	CO-2	CO-2	OO(A)	[87, 88]
	$(C_3NO_2)_{LM}$	R	0	0	—	—	—	HO(S)	[89]
	$(C_2O_4)_P$	R	0	0	—	—	—	OO(E)	[90]
B=4T	(C_6)	C_2	0	0	2+4	CC-3	CC-1	—	[1, 15, 52] [f]
	(C_5N)	C_2	0	0	2+3	CH-3	CC-1	—	[15, 91] [f] [92]
	(C_5O)	F	0	0	—	CO-2	CC-1	—	[15, 93] [f]
	$(C_4N_2)_O$	C_2	0	0	2+2	—	CN-1	—	[15, 94] [f]
	$(C_4NO)_O$	C_2	0	0	—	CC-3	CN-2(CO-2)	—	[15, 95] [f]
	$(C_4NS)_O$	C_2	0	0	—	CC-3	CN-2(CS-2)	—	[96]
	$(C_3N_3)_\Delta$	C_2	0	0	—	—	—	NN(K)	[15, 97] [f]
	$(C_3N_2O)_\Delta$	C_2	0	0	—	—	—	NO, ON(K)	[98]
	$(C_3N_2O)_{LO}$	C_2	0	0	—	—	NO-1	NO(K)	[99]
B=4U	(C_5H)	R	0	1	—	CH-2	CH-2	—	[1] [f] [101] [102]
	$(C_3N_2H)_{VO}$*	R	0	1	—	CH-2	—	—	[103]
B=5	(C_6)	R	0	0	(6)	CC-3	CC-2	—	[1, 14] [f]
	(C_5N)	R	0	0	2+3	CN-3	CC-2	—	[19]
	(C_5N)*	R	0	0	—	CN-2	CC-3	—	[104]
	(C_5O)	R	0	0	—	CO-2	CC-3	—	[100, 102, 105, 106]
With cross-bonds [g]									
$B=2'_P$	$(C_3NOM)_V$*	F	1	1	1+2	—	CN-1	—	[107]
$4'_X$	(C_5O)*	R	0	0	—	CO-2(CC-2)	—	—	[108]
$4'_T$	(C_5O)	R	0	0	—	CO-2(CC-2)	CC-3	—	[101]
2. Five-Center Model									
$B=1/\beta_2\alpha_2$	$(C_2S_2X)_{SV}$	F	1	1	—	—	—	XS(S)	[109]
	(CN_4)*	F	1	1	—	—	—	NN(E)	[110]
$B=2_V/\alpha_1\alpha_2$	(CN_4)*	(F)	1	1	—	—	—	NN(E)	[110]
$\alpha_3\alpha'_3$	(C_4N)	(C_2)	0	0	1+3	CN-2	CC-2	—	[111]
$B=2_S/\alpha_1\beta_1$	$(C_2N_2S)_{SS}$	C_3	0	0	—	—	—	SN, NN(E)	[112]
$\beta_1\alpha_1$	$(C_3NS)_V$*	F	0	0	—	CS-1	—	—	[65]
	$(C_2N_2S)_{VV}$	F	0	0	—	SN-1	—	—	[113]
	$(C_2NOS)_S$	F	0	0	—	—	—	NO(E), OS(K)	[114]
	$(C_2O_2M)_{VS}$	F	0	0	—	OO-1	—	—	[115]
	$(CN_3O)_V$*	(F)	0	0	—	—	—	ON(K)	[116]
	$(CN_3S)_V$*	F	0	0	—	—	—	NS(E)	[31]
$\alpha_2\alpha_3$	$(C_2OSH)_S$	F	0	1	—	—	—	OH(K)	[117]
	(CNOSH)	F	0	1	—	—	—	NH(K)	[118]
$B=3_V/\alpha_1\beta_1$	(C_4N)	C_2	0	0	—	CC-3	CN-2	—	[119]
	(C_4O)	C_2	0	0	1+3	CO-3	CC-2	—	[120]
	(C_4S)	C_2	0	0	—	CC-3	CS-2	—	[28]
	$(C_2PO_2)_{VS}$	C_2	0	0	—	OO-3	—	—	[121]
$\beta_1\alpha_1$	(C_5)	F	0	0	—	CC-2	CC-3	—	[29]
	(C_4P)	F	0	0	—	CP-2	CC-3	—	[122]
	(C_4S)	F	0	0	—	CS-2	CC-3	—	[28, 130]
$\alpha_2\alpha_3$	$(C_3O_2)_S$	R	1	0	—	—	OH-2	—	[123, 124]
	$(C_2NO)_{SV}$	R	1	0	—	—	—	NO(S)	[125]
	$(C_2NO_2)_{SS}$	R	1	0	—	—	—	OO(S)	[126]
$\alpha_3\alpha_2$	(C_4S)	R	1	0	1+3	HC-2	CC-2	—	[127]
	$(C_3SO)_S$	R	1	0	—	HO-2	—	OS(S)	[128]
	$(C_2N_2S)_{VV}$	R	0	1	—	—	NS-2	—	[129]

Reaction [a]		Mode [b]	σ-Transfer carbon	σ-Transfer other	Reaction Type: Construction [c]	Elimination [d]	Addition [d]	Refunctionalization [e]	Ref.
2. Five-Center Model (cont'd.)									
$B=3_S/\beta_1\alpha_1$	$(C_3S_2)_S$	C_2	0	0	—	—	SS-1	—	[131]
$\alpha_1\alpha_2$	$(C_3NO)_S$	F	0	0	—	—	—	—	[132]
	$(C_2NOS)_S$*	F	0	0	—	—	—	NO(K)	[114]
$\alpha_2\alpha_1$	(C_4N)	C_2	0	0	2+2	—	CC-1	—	[133, 134]
	(C_4O)	C_2	0	0	2+2	—	CC-1	—	[135]
	$(C_3N_2)_V$	C_2	0	0	1+2	—	CN-1	—	[129, 136]
	$(C_3NO)_V$	C_2	0	0	1+2	—	CO-1	—	[138, 139]
	$(C_3NO)_S$	C_2	0	0	1+1	—	—	ON(K)	[132, 137]
	$(C_3NS)_V$	C_2	0	0	1+2	—	CS-1	—	[114]
	$(C_2N_3)_S$	C_2	0	0	—	—	—	NN(K)	[140]
	$(C_2NPO)_V$	C_2	0	0	1+1	—	—	—	[141]
	$(C_2NOS)_S$	C_2	0	0	—	—	—	OS, SN(K)	[142, 181]
	$(CN_3O)_V$	(C_2)	0	0	—	—	—	ON(K)	[143]
$\alpha_3\beta_3$	(C_4S)	R	0	0	1+3	CS-2	CC-2	—	[144]
	$(C_3N_2)_V$	R	0	0	—	CN-2	CN-2	NN(A)	[145]
$\alpha_3\alpha'_3$	(C_5)	R	0	0	1+3	CC-2	CC-2	—	[146]
	(C_4P)	R	0	0	1+3	CP-2	CC-2	—	[147]
	(C_4P)	R	0	0	1+3	CP-2	CC-2	—	[147]
	(C_4O)	R	0	0	1+3	CO-2	CC-2	—	[148]
	(C_4S)	R	0	0	1+3	CS-2	CC-2	—	[149, 150]
	$(C_3N_2)_V$	R	0	0	—	CN-2	CN-2	NN(A)	[151]
	$(C_3NO)_V$	R	0	0	—	CN-2	CO-2	ON(A)	[152, 153]
	$(C_3PO)_V$	R	0	0	—	CO-2	CP-2	PO(A)	[154]
	$(C_3OS)_S$	R	0	0	—	OS-2	—	OH(S)	[155, 156]
	$(C_3OS)_V$	R	0	0	—	CO-2	CS-2	SO(A)	[51, 157]
	$(C_2O_2S)_{SS}$	R	0	0	—	—	—	OH(S)	[159]
$B=4/\alpha_1\alpha_2$	(C_4N)	R	0	0	1+3	CH-2	CC-2	—	[160]
	$(C_3N_2)_V$	R	0	0	1+2	—	CN-2	—	[160]
	$(C_2N_3)_V$	R	0	0	—	NN-3	—	—	[161]
	$(CN_3S)_V$	R	0	0	—	—	—	NS(E)	[31]
$\alpha_2\alpha_1$	$(C_3NO)_S$	R	0	0	—	OH-2	—	ON(E)	[132, 137]
$\alpha_2\alpha_3$	$(C_3NO)_V$	R	0	0	—	CH-2	CO-3	—	[30]
$\alpha_3\alpha_2$	(C_5)	R	0	0	(5)	CC-3	CC-2,3	—	[162]
	(C_4N)*	R	0	0	1+3	—	—	—	[163]
$\alpha_3\beta_3$	$(C_2N_3)_V$*	R	0	0	—	—	NN-3	—	[143]
With Rearrangement									
$B=2_V/\alpha_1\alpha_2$	$(C_3OH)_V\sim C$*	(F)	0	2	1+3 [h]	CH-1	—	—	[164]
	$(C_3OX)_S\sim C$	F	1	1	1+2 [h]	—	—	XO(S)	[165, 166]
	$(C_2OXH)_V\sim C$	F	0	2	1+2 [h]	—	—	—	[171]
$B=3_V/\alpha_3\alpha'_3$	$(C_3OH)_V\sim C$	R	0	1	1+3 [h]	—	CH-1	—	[167]
	$(C_2NOH)_V\sim C$	R	0	1	1+2 [h]	—	—	—	[168]
	$(C_2O_2H)_{VS}\sim C$	R	0	1	1+2 [h]	—	—	—	[169, 170]
$B=3_S/\alpha_1\alpha_2$	$(C_4O)\sim H$	(F)	0	0	—	CO-1	—	OH(K)	[172]
	$(C_3O_2)_S\sim C$	F	0	0	1+2 [h]	—	—	—	[173]
	$(C_2NOS)_S\sim C$	F	0	0	—	—	—	OS(K)	[181]
	$(C_2NOS)_S\sim H$	F	0	0	—	—	—	OS(K)	[142]
$\alpha_3\alpha'_3$	$(C_2N_3)_V\sim C$*	R	0	0	1+2 [h]	—	—	—	[174]
	$(C_2NO_2)_S\sim H$	R	0	0	—	—	—	OH(S)	[180]
$B=4/\alpha_1\alpha_2$	$(C_3N_2)_S\sim S$	R	0	0	—	—	—	SN, NN(K)	[175]
$\alpha_2\alpha_1$	$(C_3NO)_V\sim C$*	R	0	0	1+3 [h]	—	CO-2	—	[138]
$\alpha_3\alpha_2$	$(C_3N_2)_V\sim O$*	R	0	0	—	CN-3	CN-2	—	[103]
$B=5/\alpha_1\alpha_2$	$(C_5)\sim Si$	R	0	0	—	—	—	—	[176]
	$(C_5)\sim C$	R	0	0	1+5 [h]	—	—	—	[65]
	$(C_5)\sim D$	R	0	0	—	CC-3	CC-3	—	[177]
	$(C_4N)\sim C$	R	0	0	1+5 [h]	CC-3	CN-3	—	[178]

[a] Halogens collectively noted as X, metals as M, H placed last in atom lists; single subscripts following these lists are for carbon orientation of 2 or 3 carbons, other atom orientation (O, M, P) for four carbons; a second subscript for like heteroatoms appears as well in $C_{2-3}Z_{2-3}$ cases in which orientation uncertainty would otherwise exist.

[b] Mode is in parentheses for cases in which the pericyclic frame itself shows cycloaddition of two or three components (C_3, C_2, CF_3, CF_2) or fragmentations (F) into two components but the components are actually linked outside the reactive frame by a bridge [40], *e.g.* in an internal Diels-Alder reaction.

[c] Construction reactions indicated by "m+n", the number of carbons involved in each synthon is quoted (cf. Tables 8—12); cleavages are not listed.

[d] Elimination and addition follow notation of Scheme 9, *i.e.* both added and eliminated atoms are quoted, the number following (1, 2, or 3) reflecting the minimal shell bond levels of Scheme 9 ($B=1, 2_O(2_V)$, or 3_V).

[e] The first letter indicates the atom forming a new bond to carbon, the second that breaking a bond to carbon; letters in parentheses refer to the bond levels given in Tables 14 and 15: S = substitution; K = ketalization; E = ester refunctionalization; A = allylic refunctionalization.

[f] Review article.

[g] Cross-bond frames are labeled with the peripheral shell bonds only but distinguished with a prime; only the allyl-cyclopropyl interconversions of Scheme 5 are listed here, the rearrangements being listed as five-center cases (see note [h]).

[h] Rearrangements attendant on five-center reactions, corresponding to the first group in Scheme 5 but annotated as five-center models; the migrating atom is noted as ~C, ~H, *etc.* All rearrangements of carbon are formal constructions with cleavage; the construction aspect is noted in the list.

Common "Name" Reactions as Pericyclics

Reaction	Mode	Name	Reviews
$B=3_{\Delta}$	C_3	[2+2+2]-Cycloaddition	[1]
$B=3_{L}$	C_2	Ene Reaction	[63]
$3_L(C_3O_2H)_{LM}$	F	Acetate Pyrolysis	[179]
$3_L(C_3OSH)_{LM}$	F	Chugaev Reaction	[179]
$B=4_X(C_6)$	R	Cope Rearrangement	[1, 14]
$4_X(C_5Z)$	R	Claisen Rearrangements	[14, 76, 80]
$4_X(C_4N_2)$	R	Fischer Indole Synthesis	[84]
$B=4_T$	C_2	Diels-Alder Reaction	[15, 52]
$B=4_U$	R	1,5-Sigmatropic Rearrangement	[1]
$B=5$	R	Electrocyclic Reaction	[1]
$B=2_S/\beta_1\alpha_1(C_2O_2M)_{VS}$	F	Glycol Cleavage	[115]
$B=3_S/\alpha_2\alpha_1$	C_2	1,3-Dipolar Addition	[27]
$3_S/\alpha_3\alpha'_3$	R	2,3-Sigmatropic Rearrangement	[—]

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German version: Angew. Chem. 86, 71 (1974)

[1] *R. B. Woodward* and *R. Hoffmann*: The Conservation of Orbital Symmetry. Academic Press, New York 1970.

[2] *M. G. Evans* and *E. Warhurst*, Trans. Faraday Soc. *34*, 614 (1938); *35*, 824 (1939).

[3] a) *M. J. S. Dewar*, Angew. Chem. *83*, 859 (1971); Angew. Chem. internat. Edit. *10*, 761 (1971). b) Although thermal pericyclic reactions of 4n-electrons do occur [1], they are not treated here.

[4] *J. B. Hendrickson*, J. Amer. Chem. Soc. *93*, 6854 (1971). The letters for the B=2 shell correspond to *ortho* (O), *meta* (M), and *para* (P); the letters for the B=3 and 4 shells visually indicate their orientations: lines joining the midpoints of the shell bonds form the letter used in each case. As a notation the letter is used as a subscript to the number of shell bonds, *e.g.* $B=4_T$ for the Diels-Alder reaction, *etc.* The single notation letter thus serves economically to indicate aromatic substituent orientation or pericyclic reaction shell or atom combinations in that shell.

[5] *V. Boekelheide* and *E. Sturm*, J. Amer. Chem. Soc. *91*, 902 (1969).

[6] *R. Grigg*, *A. W. Johnson*, *K. Richardson*, and *K. W. Shelton*, Chem. Commun. *1967*, 1192.

[7] The numbers of C_2N_4 and CN_5 combinations are in any case the same as C_4N_2 or C_5N (Table 1). The numbers of C_2O_4 and CO_5 are also the same as these for forms with $B\leq 2$ and in $B=3_L(C_2O_4=5;\ CO_5=1)$; in $B=3_V$, 4_X and 4_T, $C_2O_4=1$ and CO_5.

[8] *A. T. Blomquist* and *L. H. Liu*, J. Amer. Chem. Soc. *75*, 2153 (1953). The intermediate is a C_2N_4 aromatic which may actually fragment either to acetylene + $2N_2$ or a dinitrile + N_2 (from the other Kekulé form); this has apparently been observed in a hindered cyclohexane derivative: *D. E. Applequist*, *P. A. Gebauer*, *D. E. Gwynn*, and *L. H. O'Connor*, J. Amer. Chem. Soc. *94*, 4272 (1972).

[9] *D. L. Clive* and *C. V. Denyer*, Chem. Commun. *1971*, 1113.

[10] *J. S. Wright*, Chem. Phys. Lett. *6*, 476 (1970).

[11] *A. M. Patterson*, *L. T. Capell*, and *D. F. Walker*: The Ring Index, 2nd Edit. Amer. Chem. Soc. (1960).

[12] Bond energies and their uncertainty and variability are discussed in: *S. W. Benson*, J. Chem. Educ. *42*, 502 (1965) and the bibliography cited therein. The values given in Table 3 were taken from *Benson*'s review and from: *J. A. Kerr* and *A. F. Trotman-Dickenson* in: Handbook of Chemistry and Physics, 51st Edit. Chemical Rubber Co., Cleveland 1970, pp. F-158—166.

[13] It must be appreciated that location of these examples in the chemical literature is generally very difficult. Major reviews are available in Refs. [14—16].

[14] *S. J. Rhoads* in *P. de Mayo*: Molecular Rearrangements. Wiley-Interscience, New York 1963. p. 655ff.

[15] *J. Hamer*: 1,4-Cycloaddition Reactions. Academic Press, New York 1967.

[16] *J. Mathieu* and *J. Valls*, Bull. Soc. Chim. Fr. *1957*, 1509.

[17] *E. Vogel* and *R. Erb*, Angew. Chem. *74*, 76 (1962); Angew. Chem. internat. Edit. *1*, 53 (1962).

[18] *J. Nieuwenhuis* and *J. F. Arens*, Rec. Trav. Chim. Pays-Bas *77*, 761 (1958).

[19] *G. Ege* and *E. Beisegel*, Angew. Chem. *80*, 316 (1968); Angew. Chem. internat. Edit. *7*, 303 (1968).

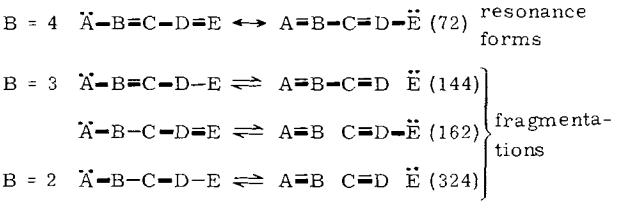
[20] *M. E. Synerholm*, *N. W. Gilman*, *J. W. Morgan*, and *R. K. Hill*, J. Org. Chem. *33*, 1111 (1968).

[21] *H. O. House* and *F. A. Richey, Jr.*, J. Org. Chem. *34*, 1430 (1969).

[22] *R. Manning*, personal communication.

[23] With respect to valency v_i, at atom i, $\Delta v_i=0$ in 5α- and 6-rings, and $\Sigma v_i=r+2B$ where r=ring size ($\max \Sigma v_i=3r$); for β-forms ($r=5$), $\Sigma v_i=r+2B+1=6+2B$.

[24] These linear fragmentations [25] may formally be analogously characterized by the ten possible shell bond combinations on five atoms with the attendant possible atom combinations overlaid. Of the ten unique shell bond combinations the first or full-shell (B=4) set is again a single resonant molecule and only three are true fragmentations, shown below. The other six shell-bond combinations (not shown) are additions of two or three components into a transition complex which subsequently fragments.



The possible atom combinations from the four valencies (*i.e.* H, O, N, and C), are totaled in parentheses for each set.

[25] *C. A. Grob* and *P. W. Schiess*, Angew. Chem. *79*, 1 (1967); Angew. Chem. internat. Edit. *6*, 1 (1967).

[26] Since more than one interconversion exists in the five-atom set for each shell/atom combination, the α or β electron-form is also indicated in the notation as $\alpha_1\beta_1$ for $\alpha_1\rightarrow\beta_1$, *etc.* The notation of shell here implies its symmetric orientation with respect to the vertical symmetry element.

[27] *R. Huisgen*, Bull. Soc. Chim. Fr. *1965*, 3431; Angew. Chem. *80*, 329 (1968); Angew. Chem. internat. Edit. *7*, 321 (1968).

[28] *S. D. Turk* and *R. L. Cobb* in Ref. [15], p. 13.

[29] *W. Dilthey*, *W. Schommer*, and *O. Trösken*, Chem. Ber. *66*, 1627 (1933).

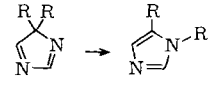
[30] *R. B. Woodward* and *D. J. Woodman*, J. Amer. Chem. Soc. *88*, 3169 (1966).

[31] *D. Martin*, Angew. Chem. *76*, 303 (1964); Angew. Chem. internat. Edit. *3*, 311 (1964).

[32] *P. Van R. Schleyer*, *G. W. Van Dine*, *U. Schöllkopf*, and *J. Paust*, J. Amer. Chem. Soc. *88*, 2868 (1966).

[33] *C. Frisell* and *S.-O. Lawesson*, Ark. Kemi *17*, 401 (1961).

[34] In fact the B=5 is now no longer a resonance example but a rearrangement corresponding to the hexagonal frame with a cross-bond on $B=4_U$ (across positions 2 on $B=4_U$ in Table 1). Hence the number of possibilities for introducing heteroatoms (N only) is increased: C_4N (3), C_3N_2—V (3), C_3N_2—S (2), C_2N_3—V (2), C_2N_3—S (3), CN_4 (2), for a total of 15 rather than 6 and an overall total of 495 instead of 486. An example of C_3N_2—S is illustrated:



[35] *J. M. Conia* and *J. Salaun*, Accounts Chem. Res. *5*, 40 (1972).

[36] *Y. Pocker* in *P. de Mayo*: Molecular Rearrangements. Wiley-Interscience, New York 1963, p. 18; *C. L. Stevens*, *T. A. Treat*, and *P. M. Pillai*, J. Org. Chem. *37*, 2091 (1972).

[37] *R. Huisgen*, Angew. Chem. *73*, 656 (1961).

[38] *R. Grigg* and *G. Shelton*, Chem. Commun. *1971*, 1247.

[39] *J. B. Hendrickson*, J. Amer. Chem. Soc. *93*, 6847 (1971).

[40] The cycloaddition of three components is seldom likely to be of synthetic value, although there are important cases in which two components are linked by bonds uninvolved in the reaction, as in certain [2+2+2] cycloadditions [1], *i.e.* $B=3_{\Delta}$.

[41] As an example, the product span C_4 implies construction of a linear four-carbon partial skeleton from two synthons of one and three carbons respectively or of two carbons each. In the former, this may be attachment of a single-carbon unit to a large molecule bearing three (linear) carbons involvable in a pericyclic transformation, or *vice versa*; the numbers of course refer only to the obligatory pericyclic carbons but either synthon may be larger than one or three carbons. The Fischer indole synthesis ($B=4_X(C_4N_2)$) is an example of the $C_4(2+2)$ combination. The concept of the product span, the minimum obligatory linear skeleton produced in a reaction, will be explored further in a forthcoming publication.

[42] Only seven combinations are noted in the text, although nine are listed. The first and the last—(1+5) and (3+3)—synthon pairs for a product span of C_6 are not included as simple constructions since they do not unite two separate carbon skeletons but only rearrange one, creating one C—C bond by breaking another; the two are the [1,5] and [3,3] sigmatropic rearrangements, respectively, *i.e.* $B=4_U$ and $4_X(C_6)$.

[43] There are some limitations on the higher shells which may be built and still contain a given partial shell. Thus 3_{Δ} cannot be created containing a 2_O partial shell, nor a 4_U from 3_{Δ}. The logical situation is exactly paralleled by the limitations on adding substituents in certain orientations to particular n-substituted benzenes and is fully explicated in the pathways graph (Fig. 2 in Ref. [2]). This graph in effect also delimits those shells which may be formed from given lower shells, since the nomenclature used is the same.

[44] This is also a logical requirement of equation (5). We impose the condition of a shell bond linking each construction carbon to its neighbor so that there are π-bonds at C=W and C≡Z, thus forbidding σ-transfer of carbon. This is a minimal obligatory shell, $B_0=2_M$, for which the product is one-component, and hence not a fragmentation. This result is maintained in any larger shell, B_0+n, containing $B_0=2_M$ as well (see Ref. [43]).

[45] The question of whether a carbene will undergo a six-electron cycloaddition to, say, a diene, rather than a four-electron cycloaddition (to form a three-membered ring) is left unanswered; the tabulations include the six-electron carbene cycloadditions as possibilities.

[46] Some of the B=3 cases have the central carbon of the three-carbon synthon acting as Q and hence the product is a carbene and the reactions are unlikely to be observable (these are asterisked).

[47] *J. B. Hendrickson* and *R. Bergeron*, Tetrahedron Lett. *1973*, 3609; it may be noted that the reaction occurs in the gas phase (in a sealed tube), enhancing the likelihood that it may be concerted.

[48] There is only one fragmentation, F-2, for the α_1 starting material (in shell $B=2_V$; cf. Table 10); this was also included in Scheme 8. The $\alpha_1 \rightarrow \beta_1$ conversion is a construction analogous to the elimination reaction (X=Z=O; Y=C) investigated by *Corey et al.* (see [49]).

[49] *E. J. Corey* and *R. A. E. Winter*, J. Amer. Chem. Soc. *85*, 2677 (1963); *87*, 934 (1965).

[50] As examples, quoted values [12] for simple C—H and O—H energies vary over a 15 kcal/mol range, while C—H and C—C values in allylic positions turn out lower than simple saturated ones by 10—15 kcal/mol; whether the latter difference is really applicable to pericyclic calculations or only reflects the experimental system used in its determination is unclear. Furthermore, values for special bonding situations of interest here (*e.g.* $>C=NR_2^{\oplus}$, $-N=C=O$, *etc.*) are not available while those for other situations ($-CO-O- \rightarrow CO_2$, 30 kcal/mol) seem out of line with qualitative experience.

[51] *D. A. Evans*, *G. C. Andrews*, and *C. L. Simms*, J. Amer. Chem. Soc. *93*, 4956 (1971).

[52] *J. Sauer*, Angew. Chem. *78*, 233 (1966); *79*, 76 (1967); Angew. Chem. internat. Edit. *5*, 211 (1966); *6*, 16 (1967); *A. S. Onishchenko*: Dienovyi Sintez. Izdatelstvo Akad. Nauk SSR, Moscow 1963; Diene Synthesis. Israel Program for Scientific Translations, Jerusalem 1964.

[53] Alternatively, the larger the calculated equilibrium ΔE the lower the activation energy in the preferred direction. The lowering of activation energy (from a model of $\Delta E \approx 0$) should be a third to a half of the substrate-product ΔE.

[54] *P. S. Wharton* and *D. H. Bohlen*, J. Org. Chem. *26*, 3615 (1961).

[55] *C. J. Harding*, *A. G. Loudon*, *A. Maccoll*, *R. G. Rodgers*, *R. A. Ross*, *S. K. Wong*, *J. Shapiro*, *E. S. Swinbourne*, *V. R. Stimson*, and *P. J. Thomas*, Chem. Commun. *1967*, 1187.

[56] *E. D. Brown*, *T. W. Sam*, and *J. K. Sutherland*, Tetrahedron Lett. *1969*, 5025.

[57] *C. W. Mortenson* and *M. A. Spielman*, J. Amer. Chem. Soc. *62*, 1609 (1940).

[58] *S. M. McElvain*, *B. E. Kent*, and *C. L. Stevens*, J. Amer. Chem. Soc. *68*, 1924 (1946).

[59] *R. L. Shriner*, *S. O. Ford*, and *L. J. Roll*, Org. Syn., Coll. Vol. II, 368 (1943).

[60] *P. I. Paetzold* and *S. Kosma*, Chem. Ber. *103*, 2003 (1970).

[61] *M. J. Betts* and *P. Yates*, J. Amer. Chem. Soc. *92*, 6982 (1970).

[62] *H. W. Moore*, *H. R. Sheldon*, *D. W. Deters*, and *R. J. Wilholm*, J. Amer. Chem. Soc. *92*, 1675 (1970).

[63] *H. M. R. Hoffmann*, Angew. Chem. *81*, 597 (1969); Angew. Chem. internat. Edit. *8*, 556 (1969).

[64] *J. K. Crandall* and *R. J. Watkins*, Tetrahedron Lett. *1967*, 1717.

[65] *D. C. De Jongh* and *G. N. Everson*, J. Org. Chem. *37*, 2152 (1972).

[66] *M. S. Newman*, *S. S. Gupte*, and *S. K. Sankarrappa*, J. Org. Chem. *35*, 2757 (1970).

[67] *J. A. Marshall* and *N. H. Andersen*, Tetrahedron Lett. *1967*, 1219; J. Org. Chem. *35*, 186, 858 (1970).

[68] *E. N. Marvell* and *B. Schatz*, Tetrahedron Lett. *1967*, 67.

[69] *A. T. Blades* and *G. W. Murphy*, J. Amer. Chem. Soc. *74*, 1039 (1952).

[70] *D. F. Detar*, Org. React. *9*, 409 (1957); cf. *C. Graebe* and *F. Ullmann*, Liebigs Ann. Chem. *291*, 16 (1896).

[71] *R. F. C. Brown*, *E. N. Cain*, *G. V. Meehan*, and *R. N. Warrener*, Tetrahedron Lett. *1967*, 5249.

[72] *P. J. Gorton* and *R. Walsh*, Chem. Commun. *1972*, 782.

[73] *D. Y. Curtin* and *A. R. Stein*, Org. Syn. *46*, 115 (1966).

[74] *S. Hauptmann*, *M. Kluge*, *K.-D. Seidig*, and *H. Wilde*, Angew. Chem. *77*, 678 (1965); Angew. Chem. internat. Edit. *4*, 685 (1965).

[75] *J. W. Wilson* and *S. A. Sherrod*, Chem. Commun. *1968*, 143.

[76] *A. Jefferson* and *F. Scheinman*, Quart. Rev. Chem. Soc. *22*, 391 (1968).

[77] *G. Opitz*, Liebigs Ann. Chem. *650*, 122 (1961).

[78] *R. K. Hill* and *N. W. Gilman*, Tetrahedron Lett. *1967*, 1421.

[79] *C. George*, *E. W. Gill*, and *J. A. Hudson*, J. Chem. Soc. *C 1970*, 74.

[80] *H. J. Hansen* and *H. Schmid*, Chimia *24*, 89 (1970).

[81] *W. J. Croxall* and *J. O. van Hook*, J. Amer. Chem. Soc. *72*, 806 (1950).

[82] *H. Kwart* and *T. J. George*, Chem. Commun. *1970*, 433.

[83] *B. W. Bycroft* and *W. Landon*, Chem. Commun. *1970*, 168, 967.

[84] *B. Robinson*, Chem. Rev. *63*, 373 (1963).

[85] *T. Sheradsky* and *G. Salemnick*, J. Org. Chem. *36*, 1061 (1971).

[86] *W. G. Young*, *I. D. Webb*, and *H. L. Goering*, J. Amer. Chem. Soc. *73*, 1081 (1951).

[87] *F. W. Bachelor* and *G. A. Miana*, Tetrahedron Lett. *1967*, 4733.

[88] *E. S. Lewis* and *J. T. Hill*, J. Amer. Chem. Soc. *91*, 7450 (1969).

[89] *H. O. House* and *F. A. Richey, Jr.*, J. Org. Chem. *34*, 1430 (1969).

[90] *M. J. Goldstein* and *H. A. Judson*, J. Amer. Chem. Soc. *92*, 4119 (1970).

[91] *R. Gompper*, Angew. Chem. *81*, 348 (1969); Angew. Chem. internat. Edit. *8*, 312 (1969).

[92] *K. Hafner*, *J. Häring*, and *W. Jäkel*, Angew. Chem. *82*, 135 (1970); Angew. Chem. internat. Edit. *9*, 159 (1970).

[93] *H. Gotthardt*, *R. Huisgen*, and *H. O. Bayer*, J. Amer. Chem. Soc. *92*, 4340 (1970).

[94] *L. Caglioti*, *G. Rosini*, *P. Tundo*, and *A. Vigevani*, Tetrahedron Lett. *1970*, 2349.

[95] *G. Kresze*, Angew. Chem. *78*, 648 (1966); Angew. Chem. internat. Edit. *5*, 614 (1966).

[96] *W. Wucherpfennig*, Tetrahedron Lett. *1967*, 3235.

[97] *H. M. Blatter*, Tetrahedron Lett. *1964*, 1087.

[98] *H. Ulrich*, Angew. Chem. *79*, 1020 (1967); Angew. Chem. internat. Edit. *6*, 1000 (1967).

[99] *D. Mackay*, *J. A. Campbell*, and *C. P. R. Jennison*, Can. J. Chem. *48*, 81 (1970).

[100] *A. Roedig*, Angew. Chem. *76*, 276 (1964); Angew. Chem. internat. Edit. *3*, 317 (1964).

[101] *P. Schiess*, Angew. Chem. *84*, 345 (1972); Angew. Chem. internat. Edit. *11*, 288 (1972).

[102] *W. H. Pirkle*, *H. Seto*, and *W. V. Turner*, J. Amer. Chem. Soc. *92*, 6984 (1970).

[103] *D. Gordon*, *L. Frye*, and *H. Sheffer*, Acta Chem. Scand. *23*, 3577 (1969).

[104] *E. N. Marvell*, *G. Caple*, and *I. Shahildi*, J. Amer. Chem. Soc. *92*, 5641, 4646 (1970).

[105] *P. Schiess* and *H. L. Chia*, Helv. Chim. Acta *53*, 485 (1970); *P. Schiess*, *R. Seeger*, and *C. Suter*, *ibid. 53*, 1713 (1970).

[106] *A. Roedig*, *G. Märkl*, and *H. Schaller*, Chem. Ber. *103*, 1011 (1970).

[107] *K. N. Campbell*, *B. K. Campbell*, *L. G. Hess*, and *I. J. Schaffner*, J. Org. Chem. *9*, 184 (1944).

[108] *W. von E. Doering* and *H. D. Roth*, Tetrahedron *26*, 2825 (1970).

[109] *D. L. J. Clive* and *C. V. Denyer*, J. C. S. Chem. Comm. *1972*, 773.

[110] *D. W. Jones*, Chem. Commun. *1970*, 1084.

[111] *L. A. Paquette* and *M. Rosen*, Tetrahedron Lett. *1967*, 703.

[112] *W. Mack*, Angew. Chem. *79*, 1106 (1967); Angew. Chem. internat. Edit. *6*, 1084 (1967).

[113] *G. Wittig* and *R. W. Hoffmann*, Angew. Chem. *73*, 435 (1961); Chem. Ber. *95*, 2718, 2729 (1962).

[114] *J. E. Franz* and *L. L. Black*, Tetrahedron Lett. *1970*, 1381.

[115] *R. L. Augustine*: Oxidation; Techniques and Applications in Organic Synthesis, Vol. 1, p. 189 (1969).

[116] *R. Grasheg*, Angew. Chem. *74*, 155 (1962); Angew. Chem. internat. Edit. *1*, 158 (1962).

[117] *C. R. Johnson*, *J. C. Sharp*, and *W. G. Phillips*, Tetrahedron Lett. *1967*, 5299.

[118] *J. C. Craig* and *K. K. Purushothaman*, Tetrahedron Lett. *1969*, 5305.

[119] *R. Apel* and *O. Büchner*, Angew. Chem. *74*, 430 (1962); Angew. Chem. internat. Edit. *1*, 333 (1962).

[120] *D. L. Storm* and *T. A. Spencer*, Tetrahedron Lett. *1967*, 1865.

[121] *F. Ramirez* and *N. B. Desai*, J. Amer. Chem. Soc. *82*, 2652 (1960); *85*, 3252 (1963).

[122] *F. B. Clarke* and *F. H. Westheimer*, J. Amer. Chem. Soc. *93*, 4541 (1971).

[123] *V. Rosnati*, *F. Sannicolo*, and *G. Zeechi*, Tetrahedron Lett. *1970*, 599.

[124] *K. Schank*, Chem. Ber. *103*, 3093 (1970).

[125] *A. F. Hegarty*, *J. A. Kearney*, *M. P. Cashman*, and *F. L. Scott*, Chem. Commun. *1971*, 689.

[126] *O. Schöllkopf* and *I. Hoppe*, Tetrahedron Lett. *1970*, 4527.

[127] *J. F. Biellmann* and *J. B. Ducep*, Tetrahedron Lett. *1970*, 2899.

[128] *M. Takaku*, *Y. Hayasi*, and *H. Nozaki*, Tetrahedron *26*, 1243 (1970).

[129] *W. Barbieri*, *L. Bernardi*, *P. Masi*, *L. Caglioti*, and *G. Rosini*, Tetrahedron Lett. *1970*, 1343, 1347.

[130] *M. P. Cava* and *R. L. Shirley*, J. Amer. Chem. Soc. *82*, 654 (1960).

[131] *H. D. Hartzler*, J. Amer. Chem. Soc. *92*, 1412, 1413 (1970).

[132] *R. Huisgen* and *E. Funke*, Angew. Chem. *79*, 320 (1967); Angew. Chem. internat. Edit. *6*, 365 (1967).

[133] *R. Huisgen*, *H. Gotlhardt*, *H. O. Bayer*, and *F. C. Schaefer*, Chem. Ber. *103*, 2356, 2368, 2611, 2625, 2639 (1970).

[134] *H. Gotlhardt*, *R. Huisgen*, and *H. O. Bayer*, J. Amer. Chem. Soc. *92*, 4340 (1970).

[135] *D. R. Arnold* and *L. A. Karnischky*, J. Amer. Chem. Soc. *92*, 1404 (1970).

[136] *J. Jaz* and *W. Millet*, Tetrahedron Lett. *1967*, 2777.

[137] *U. Schöllkopf* and *R. Schröder*, Angew. Chem. *84*, 289 (1972); Angew. Chem. internat. Edit. *11*, 311 (1972).

[138] *U. Strauss*, *H. P. Härter*, *M. Nevenschwander*, and *O. Schindler*, Helv. Chim. Acta *55*, 771 (1972).

[139] *O. Tsupe*, *M. Tashiro*, and *Y. Nishihara*, Tetrahedron Lett. *1967*, 3769.

[140] *R. Grasheg*, *H. Leitermann*, *R. Schmidt*, and *K. Adelsberger*, Angew. Chem. *74*, 491 (1962); Angew. Chem. internat. Edit. *1*, 407 (1962).

[141] *R. Huisgen* and *J. Wulff*, Tetrahedron Lett. *1967*, 917.

[142] *D. S. Black* and *K. G. Watson*, Angew. Chem. *84*, 34 (1972); Angew. Chem. internat. Edit. *11*, 47 (1972).

[143] *R. G. Grasheg*, Angew. Chem. *74*, 155 (1962); Angew. Chem. internat. Edit. *1*, 158 (1962).

[144] *J. E. Baldwin* and *J. A. Walker*, Chem. Commun. *1972*, 354.

[145] *J. E. Baldwin*, *J. E. Brown*, and *G. Hoefle*, J. Amer. Chem. Soc. *93*, 788 (1971).

[146] *J. E. Baldwin* and *F. J. Urban*, Chem. Commun. *1970*, 165.

[147] *J. E. Baldwin* and *C. H. Armstrong*, Chem. Commun. *1970*, 631.

[148] *J. E. Baldwin*, *J. DeBernardis*, and *J. E. Patrick*, Tetrahedron Lett. *1970*, 353; J. Amer. Chem. Soc. *93*, 3556 (1971).

[149] *E. Hunt* and *B. Lythgoe*, Chem. Commun. *1972*, 757.

[150] *J. E. Baldwin*, *R. E. Hackler*, and *D. P. Kelly*, Chem. Commun. *1968*, 537, 538, 1083.

[151] *J. E. Baldwin*, *J. E. Brown*, and *R. W. Cordell*, Chem. Commun. *1970*, 31.

[152] *A. C. Cope* and *P. H. Towle*, J. Amer. Chem. Soc. *71*, 3427 (1949).

[153] *M. Moriwaki*, *S. Sawada*, and *Y. Inouye*, Chem. Commun. *1970*, 419.

[154] *A. I. Pudovik*, *I. M. Aladzheva*, and *L. V. Spirina*, Zh. Obshch. Khim. *37*, 700 (1967).

[155] *A. Terada* and *Y. Kishada*, Chem. Pharm. Bull. *18*, 505 (1970).

[156] *U. Schöllkopf*, *J. Schössig*, and *G. Ostermann*, Liebigs Ann. Chem. *737*, 158 (1970).

[157] *R. Tang* and *K. Mislow*, J. Amer. Chem. Soc. *92*, 2100 (1970).

[158] *S. Tamagaki*, *S. Kozuka*, and *S. Oae*, Tetrahedron *26*, 1795 (1970).

[159] *S. Glue*, *I. T. Kay*, and *M. R. Kipps*, Chem. Commun. *1970*, 1158.

[160] *Y. Tamura*, *N. Tsujimoto*, *Y. Sumida*, and *M. Ikeda*, Tetrahedron *28*, 21 (1972).

[161] *S. Hauptmann*, *H. Wilde*, and *K. Moser*, Tetrahedron Lett. *1967*, 3295.

[162] *S. N. Staley* and *J. P. Erdman*, J. Amer. Chem. Soc. *92*, 3832 (1970).

[163] *D. Lednicer* and *D. E. Emmert*, J. Heterocycl. Chem. *7*, 575 (1970).

[164] *L. Bang*, *I. G. Guest*, and *G. Ourisson*, Tetrahedron Lett. *1972*, 2089.

[165] *J. Salaun* and *J. M. Conia*, Tetrahedron Lett. *1968*, 4545.

[166] *J. E. Baldwin* and *J. E. Gano*, Tetrahedron Lett. *1969*, 1101.

[167] *H. H. Wasserman*, *R. E. Cochoy*, and *M. S. Baird*, J. Amer. Chem. Soc. *91*, 2375 (1969).

[168] *J. M. Conia* and *J. Salaun*, Accounts Chem. Res. *5*, 40 (1972).

[169] *C. L. Stevens*, *T. A. Treat*, and *P. M. Pillai*, J. Org. Chem. *37*, 2091 (1972).

[170] *W. H. Urry*, *J. C. Duggan*, and *M. H. Pai*, J. Amer. Chem. Soc. *92*, 5785 (1970).

[171] *A. J. Sisti*, J. Org. Chem. *35*, 2670 (1970).

[172] *R. W. LaRochelle* and *B. M. Trost*, Chem. Commun. *1970*, 1353.

[173] *J. C. Leffingwell*, Synth. Commun. *2*, 105 (1972).

[174] *A. Hassner* and *J. S. Teeter*, J. Org. Chem. *35*, 3397 (1970).

[175] *V. P. Shah*, *R. Ketcham*, *K. J. Palmer*, and *R. Y. Wong*, J. Org. Chem. *37*, 2155 (1972).

[176] *A. J. Ashe, III*, J. Amer. Chem. Soc. *92*, 1233 (1970).

[177] *H. Tanida*, *Y. Hata*, and *H. Ishitobi*, Tetrahedron Lett. *1967*, 361.

[178] *H. Adkins* and *H. L. Coonradt*, J. Amer. Chem. Soc. *63*, 1567 (1941).

[179] *C. H. de Puy*, Chem. Rev. *60*, 431 (1960).

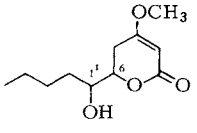
[180] *S. Tamagaki*, *S. Kozuka*, and *S. Oae*, Tetrahedron *26*, 1795 (1970).

[181] *R. Huisgen*, *W. Mack*, and *E. Anneser*, Angew. Chem. *73*, 656 (1961).

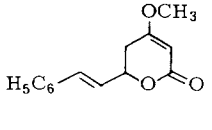
Synthesis of (±)-Pestalotin and (±)-Epipestalotin and of Optically Pure (−)-Pestalotin by Asymmetric Synthesis[**]

By *Dieter Seebach* and *Hartmut Meyer*[*]

Kimura et al.[1] isolated pestalotin *(1)*, which is a synergist of gibberellin, from the phytopathogenic fungus *Pestalotia cryptomeriaecola*. *Ellestad et al.*[2] obtained the same compound (LL-P880α) from the unidentified *Penicillium* species of Lederle culture P880. They established the (6-*S*, 1′-*S*)-configuration *(1a)* as probable for their material ($[\alpha]_D = -86.2°$), and meanwhile isolated two further dihydro-1′-hydroxy-4-methoxypyrones as metabolites from the same source[3]. Dihydromethoxypyrones occur in many other natural sources, *e.g.* kawain *(2)* in kawa root. Such compounds have hitherto been prepared by Reformatsky synthesis from 4-bromo-3-crotonic esters[1,4] or by way of hydroxypropiolic esters[5].



(1a), *threo*
(1b), *erythro*



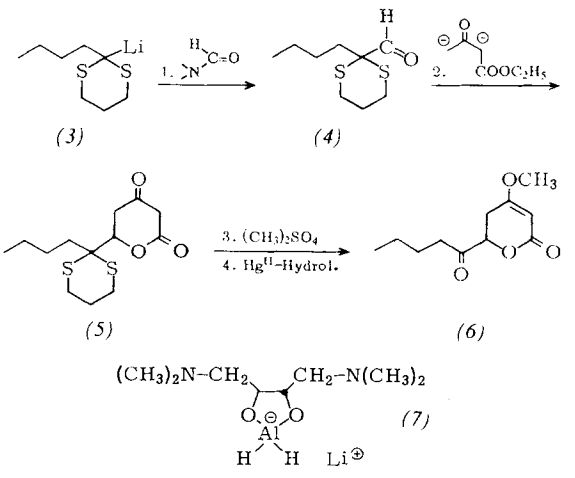
(2)

We report here a simple method of preparing *(1)* in good yield; it is applicable to analogs and enables (±)- as well as (+)- and (−)-pestalotin *(1a)* and the diastereoisomeric epipestalotin *(1b)* to be obtained.

The synthesis of didehydropestalotin *(6)* and experimental details[6] are shown in Scheme 1. The key step is treatment of the aldehyde *(4)* with the dianion[7] of acetoacetic ester, which affords the oxo lactone *(5)* directly after work-up. Conversion into the enol ether and hydrolysis of the thioacetal group by Hg(II) provides the (±)-ketone *(6)* [total yield *(4)*→*(6)*: 59%].

Hydrogenation of *(6)* by $NaBH_4$ in 2-propanol leads to a 1:1.2 mixture (>95%) of (±)-epipestalotin *(1b)* and (±)-pestalotin *(1a)*, which are eluted in that order in *ca.* 80% yield from a silica gel column by ether. The NMR spectra of (±)-*(1a)* (m.p. 82°C) and (±)-*(1b)* [m.p. 71°C, mixed m.p. with *(1a)* 56—62°C] differ mainly in the shift of the 1′-H signal, which has been given[1,2] for (−)-pestalotin as δ = 3.65, whereas for *(1b)* it appears at 3.90.

For the preparation of optically active pestalotin we reduced *(6)* with the chirally modified lithium hydridoaluminate *(7)*[8] in ether at −78°C, which gave an optical yield of *ca.* 10%. The optically active pestalotin *(1a)* was separated as described above from the epipestalotin *(1b)*, which was also optically active. On recrystallization from ether/pentane, (±)-*(1a)* became enriched in the crystals, and the active material in the mother liquor whence it was isolated in optically pure



Scheme 1. Synthesis of *(6)*. 1. *(3)* is treated in THF at −78°C with 2 equiv. of DMF, yielding *(4)* (95% yield, b.p. 71—75°C/0.06 torr). 2. After reaction of *(4)* with the acetoacetic ester dianion (1:2) for 30 min in THF at −78°C the mixture is poured into the five-fold volume of water, stirred for 12 h, acidified, and *(5)* is extracted with CH_2Cl_2 [80% yield, m.p. 129—131°C (dec)]. 3. Treating a 7% solution of *(5)* in acetone with 1.2 equiv. of $(CH_3)_2SO_4/K_2CO_3$ for 3 h gives the dithiane derivative of *(6)* (81% yield, m.p. 125.5°C). 4. A 4% solution of this derivative in 95% aqueous CH_3OH is boiled for 1.5 h with 1.2 equiv. each of $HgCl_2$ and HgO; the solution is filtered, diluted with 0.05 N HCl (1:1) and stirred for 12 h; part of the *(6)* crystallizes and the remainder is obtained by working up with CH_2Cl_2 (91% yield, m.p. 83°C).

state. On use of (*S*,*S*)-*(7)* prepared from (*R*,*R*)-tartaric acid, (+)-*(1a)* (*e.g.* $[\alpha]_D = +63.5°$) was obtained, and use of (*R*,*R*)-*(7)* led to (−)-*(1a)* {$[\alpha]_D = -85.0°$ (c = 0.76, CH_3OH), m.p. 80.5—81.0°C, mixed m.p. with (±)-*(1a)* 74—78°C}, whose spectroscopic data (UV, IR, NMR, ORD and MS) all agreed with those of the natural product[1,2]

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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

[1] *Y. Kimura, K. Katagiri*, and *S. Tamura*, Tetrahedron Lett. *1971*, 3137; Agric. biol. Chem. [Tokyo] *36*, 1925 (1972).

[2] *G. A. Ellestad, W. J. McGahren*, and *M. P. Kunstmann*, J. Org. Chem. *37*, 2045 (1972).

[3] *W. J. McGahren, G. A. Ellestad, G. A. Morton*, and *M. P. Kunstmann*, J. Org. Chem. *38*, 3542 (1973). We thank Dr. *Ellestad* for a copy of the manuscript prior to publication.

[4] *M. W. Klohs, F. Keller*, and *R. E. Williams*, J. Org. Chem. *24*, 1829 (1959); *K. S. Viswanathan* and *S. Swaminathan*, Proc. Indian Acad. Sci. *52A*, 63 (1960); *C. Piantadosi* and *V. G. Skulason*, J. Pharm. Sci. *58*, 902 (1964).

[5] *E. M. F. Fowler* and *H. B. Henbest*, J. Chem. Soc. *1950*, 3642.

[6] All the new substances gave correct elemental analyses and the expected spectra.

[7] *S. N. Huckin* and *L. Weiler*, Tetrahedron Lett. *1971*, 4835.

[8] *D. Seebach* and *H. Daum*, unpublished work; *H. Daum*, Dissertation, Universität Giessen 1973; cf. also *D. Seebach et al.*, Angew. Chem. *81*, 1002 (1969); Angew. Chem. internat. Edit. *8*, 982 (1969).

A New Type of Model Nucleotide: 5′-Deoxy-5′-adenosineacetic Acid[**]

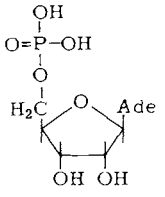
By *Hartmut Follmann*[*]

Few suitable model compounds have so far been available for structure-activity investigations of biochemically important

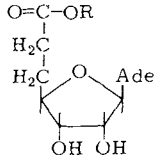
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[**] This work was partly supported by the Deutsche Forschungsgemeinschaft. I thank Mrs. *I. Kuntz* and *W. Meyer* for some of the measurements.

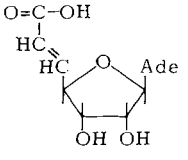
mononucleotides such as adenosine 5'-phosphate [AMP, *(1)*]. From "adenosine-5'-aldehyde", the dialdose derived from adenosine, we have recently synthesized[2], among other 5'-*C*-alkyl derivatives, adenine-9-(5',6'-dideoxy-β-D-riboheptofuranuronic acid) *(2a)*[1] and its *trans*-5',6'-didehydro compound *(3)* which have substituents containing two additional C atoms attached to C-5'. Unlike the short-chain uronic acids ("adenosine-5'-acid")[3] and the longer-chain 5'-*O*-(carboxymethyl)nucleosides[4], these new adenosine derivatives are model nucleotides that correspond exactly to the natural nucleotides but contain a carboxylate group in place of the phosphoric ester group, and resist hydrolysis. We have found that these carboxylic acids can replace AMP as building unit in oligonucleotides and as enzyme substrates.



(1)



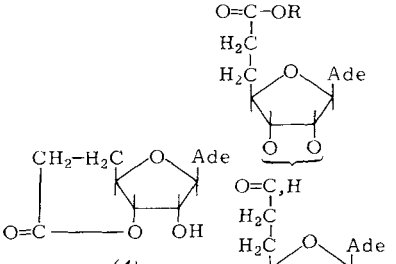
(2a), R = H
(2b), R = C_2H_5



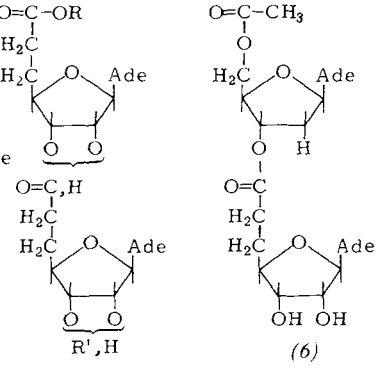
(3)

Ade = Adenine

When *(2a)* (0.1 M in pyridine) is condensed with itself or with an equivalent amount of the ethyl ester *(2b)* in the presence of dicyclohexylcarbodiimide under the conditions of a dinucleoside phosphate synthesis[5], there is formed, besides the lactone *(4)*, the dimer *(5a)* (25% yield) or *(5b)* [20% together with 10% of *(5a)*], respectively, as 2'(3')-isomer mixtures; these products are comparable with the dinucleotide pApA or the dinucleoside phosphate ApA. A small amount (<5%) of the trimeric diester *(5c)* can also be isolated. If *(2a)* is esterified with 5'-*O*-acetyl-2'-deoxyadenosine, there results the homogeneously linked nucleoside ester *(6)*[6].



(4)



R', H

(6)

Ade = Adenine *(5a)*, R = R' = H
(5b), R = C_2H_5, R' = H
(5c), R = H, R' = [*(2a)*-H]

Like the conversion of *(1)* into oligoadenylic acids, the condensation of *(2a)* to give *(5a)*—*(5c)* is accompanied by strong hypochromism of the UV absorption band and an intense longwave Cotton effect in the CD spectrum. Both effects are equal or very similar to the corresponding values for ApA and ApApA (Table 1). The compounds must therefore have conformations with comparably strong, intramolecular stacking of the bases which depends only on a suitable distance between the adenine rings and not on the structure or charge of the linking units[7].

The enzyme AMP aminohydrolase (EC 3.5.4.6) from rabbit muscle deaminates the carboxylic acids *(2a)* and *(3)* to the inosine derivatives only slightly more slowly than it converts the natural substrate *(1)* (AMP) (Table 2). The K_m value for *(2a)* is increased to only 2.7 times that for AMP, and

Table 1. Hypochromism H [a], molar ellipticity [Θ] and wavelength λ_1 of the Cotton effect [b] of *(1)*—*(5)*.

	H	[Θ]	λ_1 [nm]		H	[Θ]	λ_1 [nm]
(2a)	—	− 2000	256	*(1)*	—	− 4000	258
(4)	—	− 5000	250				
(5a)	11%	+28000	271	ApA	11%	+30000	272
(5b)	12%	+25000	271				
(5c)	15%	+35000	271	ApApA	14%	+50000	272

[a] Measured in the absorption maximum (258 nm) after alkaline hydrolysis.
[b] In unbuffered solution, pH = 6.

for the more rigidly structured *(3)* only 4.5 times. With 28% of the V_{max} value of AMP, *(2a)* is in fact a better substrate than 5'-deoxy-5'-adenosinemethanephosphonic acid[8] which is also isosteric with AMP. On the other hand, the short-chain uronic acid derived from adenosine has no biochemical activity as substrate or inhibitor of the enzyme. In view of the reaction mechanism, which has been studied several times[9], these results constitute direct proof that a monoanion at a definite distance from the adenine base is the determining structural element of a substrate for binding and catalysis by AMP

Table 2. Reaction velocity (V_{max}) and Michaelis constants (K_m) for substrates of AMP aminohydrolase in Tris: morpholinoethanesulfonic acid buffer pH = 6.0, 0.2 M in KCl, at 30°C.

Substrate	*(1)*	*(2a)*	*(3)*
V_{max} [μmol·min^{-1}·mg^{-1}]	500	140	100
K_m [mmol·l^{-1}]	0.28	0.76	1.25

aminohydrolase. This presupposes a similar *anti*-conformation of the base in *(1)*, *(2)* and *(3)*, which in fact can be demonstrated in the NMR spectra of the compounds in dilute aqueous solution[10].

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[1] Nucleosides with additional CH_2 groups between C-4' and the terminal CH_2OH group are also termed "homonucleosides" (cf. Ref. [8]). However, we consider 5'-deoxy-5'-adenosineacetic acid a better name for *(2a)* because it is short and shows unambiguously the relation to adenosine.

[2] *T. E. Walker, H. Follmann*, and *H. P. C. Hogenkamp*, Carbohyd. Res. *27*, 225 (1973).

[3] See, *e.g., H. J. Fritz, R. Machat*, and *R. R. Schmidt*, Chem. Ber. *105*, 642 (1972).

[4] *J. P. Coat* and *S. David*, C. R. Acad. Sci. *268*, 1160 (1969).

[5] *H. Follmann*, Tetrahedron Lett. *1967*, 2113.

[6] The structures of *(4)*—*(6)* follow unambiguously from the products of their alkaline hydrolysis and of their periodate degradation with subsequent alkaline fission, as well as from their electrophoretic mobilities at pH 6. R_F values on paper chromatography in ethanol/1 M ammonium acetate (5:2): *(2a)* 0.40, *(4)* 0.77, *(5a)* 0.30, *(5b)* 0.65, *(5c)* 0.16, *(6)* 0.68.

[7] Cf. *H. Follmann, H. J. Wieker*, and *H. Witzel*, Eur. J. Biochem. *1*, 243 (1967). The polymer of *(2a)*, preparation of which is, however, made difficult by low solubility and the necessary protection of the 2'-OH group, should therefore be a model compound with a neutral ester backbone that resembles poly(A) even more closely than the recently described poly[3'-*O*-(carboxymethyl)-2'-deoxyadenosine] (*A. S. Jones, M. MacCoss*, and *R. T. Walker*, Biochim. Biophys. Acta *294*, 365 (1973)).

[8] *A. Hampton, T. Sasaki*, and *B. Paul*, J. Amer. Chem. Soc. *95*, 4404 (1973).

[9] *C. L. Sielke* and *C. H. Suelter*, J. Biol. Chem. *246*, 1313 (1971).

[10] *H. Follmann* and *G. Gremels*, unpublished work.

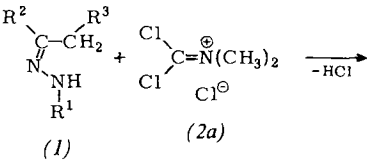
Substituted 5-Dialkylaminopyrazoles from Hydrazones and Phosgeneimonium Salts[1]

By *Thérèse van Vyve* and *Heinz Gunter Viehe*[*]

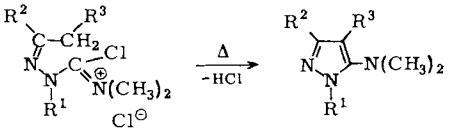
Phosgeneimonium salts (dichloromethyleneammonium salts) *(2)* react easily with nucleophiles such as amines, alcohols[2], amides[3], and compounds containing activated CH-bonds[4]. *N*-Monosubstituted hydrazones *(1)* have now been found to react with phosgeneimonium salts such as dichloromethyleneammonium chloride *(2a)* to give the substituted 5-dialkylaminopyrazoles *(4)*[5].

Primary condensation of *(2)* with the secondary amino group of *(1)* leads to formation of the new semicarbazone derivatives *(3)*, which subsequently cyclize either spontaneously on reflux or on heating to give *(4)*. Examples are listed in Table 1.

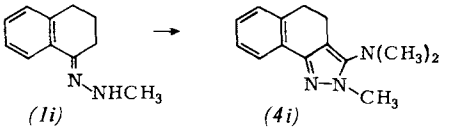
Reaction stops at the semicarbazide chloride stage *(3j)* when cyclohexanone methylhydrazone is condensed with 1-dichloromethylene-4-methylpiperazine-1,4-diylium dichloride *(2b)*; prolonged refluxing with $POCl_3$ leads to formation of the pyrazole derivative *(4j)*. *(3j)* can be converted into the semicarbazone and thiosemicarbazone.



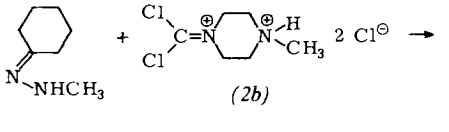
(1) *(2a)*



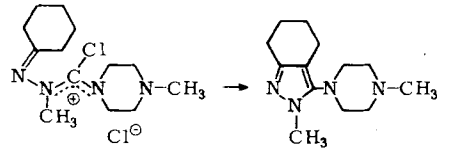
(3) *(4)*



(1i) *(4i)*



(2b)



(3j) *(4j)*

Table 1. Pyrazoles *(4)* prepared from hydrazones *(1)* and phosgeneimonium salt *(2a)*. All pyrazoles gave correct mass spectra.

(4)	R^1	R^2	R^3	Yield [%]	NMR ($CDCl_3$) (δ, TMS = 0)	IR (film) [cm^{-1}]
a	CH_3	C_2H_5	CH_3	81	1.25 (3H/t), 2.2 (3H/s), 2.8 (2H/quad.), 3.1 (6H/s), 4.03 (3H/s), 14.0 (1H$^+$) [a]	2980, 2940, 2880, 1650, 1570, 1530, 1450, 1430
b	C_6H_5	C_2H_5	CH_3	87	1.00 (3H/m), 1.6 (3H/s), 2.3 (2H/m), 3.1 (6H/s), 6.9–7.3 (5H/2m)	2980, 2940, 2880, 1640, 1620, 1600, 1560, 1460, 1430, 1410, 1330
c	CH_3	CH_3	C_2H_5	70	1.1 (3H/t), 2.1 (3H/s), 2.45 (2H/m), 2.75 (6H/s), 3.6 (3H/s)	2960, 2940, 2870, 1640, 1565, 1540, 1490, 1450, 1410, 1380
d	CH_3	C_6H_5	H	24	2.6 (6H/s), 3.65 (3H/s), 6.00 (1H/s), 7.1–7.9 (5H/2m)	2990, 2940, 2860, 2790, 1660, 1550, 1515, 1480, 1450
e	CH_3	$-(CH_2)_3-$		66	2.5 (6H/m), 2.7 (6H/s), 3.55 (3H/s)	2940, 2850, 2780, 1650, 1580, 1490, 1450, 1420, 1380
f	CH_3	$-(CH_2)_4-$		82	1.7 (4H/m), 2.5 (4H/m), 2.65 (6H/s), 3.5 (3H/s)	2920, 2840, 2780, 1660, 1610, 1580, 1565, 1510, 1440, 1420, 1380
g	CH_3	$-(CH_2)_5-$		84	1.7 (6H/m), 2.55 (4H/m), 2.75 (6H/s), 3.5 (3H/s)	2910, 2840, 2780, 1660, 1570, 1490, 1440, 1380
h	CH_3	$-(CH_2)_6-$		84	1.45 (8H/m), 2.55 (4H/m), 2.7 (6H/s), 3.55 (3H/s)	2980, 2920, 2850, 2780, 1570, 1480, 1440
i	[b]			76	2.75 (6H/s), 2.8 (4H/s), 3.65 (3H/s), 7.1 and 7.7 (4H/2m)	3050, 2930, 2840, 2780, 2680, 1610, 1580, 1560, 1490, 1450, 1380
j	[c]			37	1.7–1.9 (4H), 2.40–2.70 (11H), 3.05–3.42 (4H), 3.75 (3H)	2930, 1650, 1565, 1445, 1380, 1284, 1141, 1009

[a] Hydrochloride
[b] See formula; m.p. 44.9 °C.
[c] *(2b)* used for the preparation.

5-Dialkylaminopyrazoles (4)

Hydrazone *(1)* (1 mol) in chloroform solution is added dropwise at room temperature to the stirred suspension of *(2a)* (1 mol) in the same solvent. Stirring is continued under reflux until all *(2a)* is dissolved. The intermediary *(3)* is cyclized on prolonged refluxing (3—10 hours) in chloroform or on heating in the dry state to about 100 °C for 2 h. The solution of *(4)* in chloroform or methylene chloride is then treated with aqueous alkali; after separation the organic layer is dried with potassium carbonate. Most of the pyrazoles *(4)* can be purified by bulb-to-bulb vacuum distillation.—*(4j)*, on the other hand, is prepared *via (3j)* by refluxing *(2b)* (5.08 g, 20 mmoles) and cyclohexanone methylhydrazone (2.52 g, 20 mmoles) in 30 ml dry $CHCl_3$ for 30 minutes. After removal of solvent the residue is refluxed in 50 ml freshly distilled $POCl_3$ for 8 h. Finally, the residue is dissolved in a little water at 0 °C and treated with an excess of solid K_2CO_3. Extraction with CH_2Cl_2 and bulb-to-bulb distillation gives 1.72 g (37%) of *(4j)*.

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[1] Immonium Chemistry, Part 10.—Part 9: *H. G. Viehe, Z. Janousek, R. Gompper*, and *D. Lach*, Angew. Chem. *83*, 581 (1973); Angew. Chem. internat. Edit. *12*, 567 (1973).

[2] *H. G. Viehe* and *Z. Janousek*, Angew. Chem. *83*, 614 (1971); Angew. Chem. internat. Edit. *10*, 573 (1971).

[3] *Z. Janousek* and *H. G. Viehe*, Angew. Chem. *83*, 615 (1971); Angew. Chem. internat. Edit. *10*, 574 (1971).

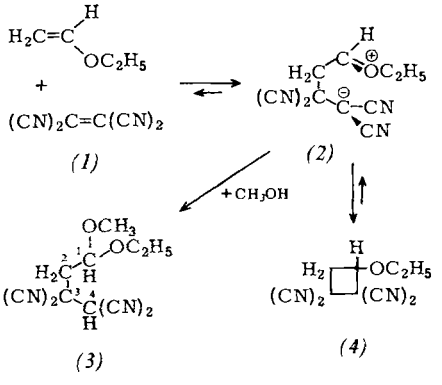
[4] *H. G. Viehe, Z. Janousek*, and *M. A. Deffrenne*, Angew. Chem. *83*, 616 (1971); Angew. Chem. internat. Edit. *10*, 575 (1971).

[5] Non-aminated 4-pyrazolecarbaldehydes are formed from *(1)* and DMF/$POCl_3$: *M. A. Kira, H. O. Abdel-Rahman*, and *K. Z. Gadalla*, Tetrahedron Lett. *1969*, 109.

Trapping of the 1,4-Dipole Formed in the 2+2-Cycloaddition of Tetracyanoethylene to Enol Ethers

By *Rolf Huisgen, Reinhard Schug*, and *Gerd Steiner*[*]

The 2+2-cycloadditions of tetracyanoethylene *(1)* to *cis-trans*-isomeric enol ethers, leading to cyclobutanes, are not highly stereospecific[1]; the intermediates capable of rotation are formed reversibly[2]. The additions of *(1)* to various enol ethers in acetonitrile occur 2600—29000 times faster than in cyclohexane[3]; from the dependence of the rate constants on solvent polarity, and from the dipole moments of the reactants, it is possible to calculate the dipole moments of the transition states, which amount to two-thirds of the values estimated for zwitterions of type *(2)*[3]. The influence of structural variation of the enol ether on the rate constants[4], the activation parameters[5] and the solvent dependence of the activation volume[6] also indicate zwitterionic intermediates in these 2+2-cycloadditions of *(1)*.



Scheme 1

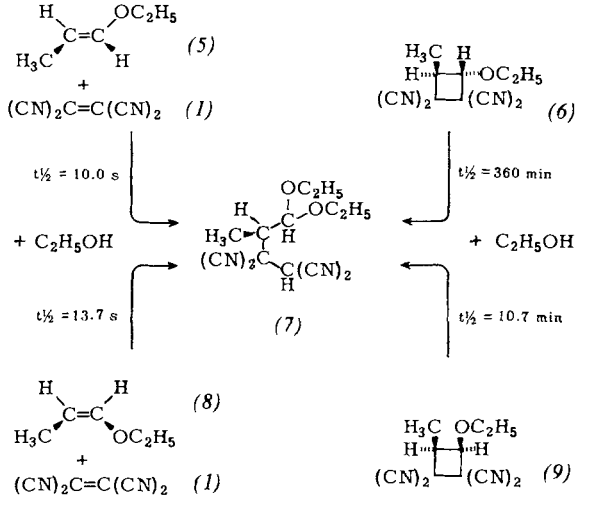
Since kinetic evidence never proves a reaction mechanism but only allows exclusion of other conceivable routes, we sought chemical proof by trapping the intermediates with reagents which are not able to combine with the reactants. Alcohols proved suitable; *(1)* is sufficiently stable in pure alcohols in the cold[**].

Whereas *(4)* is formed quantitatively from *(1)* and ethyl vinyl ether in aprotic media[7], the reaction in ice-cold methanol leads to 70% of the 1:1:1 adduct *(3)* together with 30% of *(4)* (Scheme 1) [^{1}H-NMR spectrum ($CDCl_3$) of *(3)*: $\tau = 6.56$ (s, OCH_3), OCH_2CH_3 as an ABX_3 system at 6.26, 6.37 and 8.73; 4.96 (s, 4-H), 5.23 (t, 1-H), 7.42 (d, 2-H_2)]. Owing to the acidity of the 4-H, *(3)* dissolves in aqueous sodium carbonate and is reprecipitated by acid. The acetals of Table 1 are obtained analogously by reaction of enol ethers with *(1)* and alcohols; these 1:1:1 adducts are characterized by elemental analyses and spectra.

Is it true that the zwitterionic intermediate *(2)* is trapped by alcohol or does the acetal *(3)* arise by alcoholysis of the cyclobutane *(4)*? *(4)* is in fact converted into *(3)* by methanol, but in a slower reaction which presumably occurs *via* the same 1,4-dipole *(2)*. We have previously described the slow equilibration of the *cis-trans*-isomeric cyclobutanes *(6)* and *(9)* in the polar aprotic solvent acetonitrile[1]. In Scheme 2 are collected the half-reaction times at 25 °C for the reactions of *(1)* with ethyl *trans-* *(5)* and *cis*-propenyl ether *(8)* (0.25 mol/l) in ethanol [determined by photometry of the orange charge-transfer complex of *(1)* and ethanol] and for the ethanolysis of *(6)* and *(9)*, followed by NMR spectroscopy. The formation of the acetal *(7)* from *(5)* or *(8)* with *(1)* is 2200 and 47 times faster than the one by ethanolysis of the epimeric cyclobutanes *(6)* and *(9)*. Thus, ethanol does indeed trap an intermediate in the course of the 2+2-cycloaddition of *(1)* to enol ethers.

Table 1. Acetalic interception products of type *(3)* from enol ethers, tetracyanoethylene and alcohols.

Enol ethers	Alcohol	1:1:1-Adducts M.p. [°C]	$\tau_{1\text{-H}}$	$\tau_{4\text{-H}}$
Ethyl vinyl ether	Ethanol	Oil	5.17	4.93
Ethyl vinyl ether	Methanol	Oil	5.23	4.96
Ethyl propenyl ether	Ethanol	60—61	5.45	4.71
Methyl propenyl ether	Methanol	92—93	5.63	4.81
Ethyl propenyl ether	Methanol	52—54	5.57	4.77
Methyl propenyl ether	Ethanol	95—96	5.56	4.79
Methyl propenyl ether	2-Propanol	99—100	5.32	4.31
Methyl propenyl ether	*tert*-Butyl alcohol	117—120	5.21	4.22
Ethyl 1-isobutenyl ether	Ethanol	79—80	5.63	4.70
3,4-Dihydro-2*H*-pyran	Ethanol	109—110	5.41	4.55



Scheme 2

A final objection: Perhaps the acetalic 1:1:1 adducts might not be formed from 1,4-dipoles of type *(2)*, *i.e.* not by interception of intermediates in the formation of cyclobutanes, but instead in some unknown (although difficultly conceivable) manner from the three components. If this were the case, then this route *x* must be so fast that it suppresses the 2+2-cycloaddition since ring opening of the cyclobutanes in alcohol is much slower. Kinetic measurements show that enol ethers react with *(1)* in alcohols *more slowly* than is assumed for the 2+2-cycloadditions. The expected values are based on the linear relations between $\log k_2$[3] and the empirical parameter E_T of the solvent polarity[8]. According to the extrapolation, *e.g.* for 3,4-dihydro-2*H*-pyran, the reaction with *(1)* in ethanol and methanol should be 38 and 880 times faster than in acetonitrile. However, Table 2 reveals that four enol ethers in alcohols give smaller rate constants than in acetonitrile. This decrease of the rate constant in alcohols is often observed in cases of specific solvation of a reactant by hydrogen bonding with alcohols[9, 10].

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[**] *R. H.* thanks Dr. *H. E. Simmons*, E. I. Du Pont de Nemours and Co., Wilmington (USA), for providing this information in July 1971.

Table 2. Rate constants of the reactions of *(1)* with enol ethers in alcohols (to give dialkyl acetals) and in acetonitrile (to give 2+2-cycloadducts) at 25 °C.

Enol ether	Solvent	$10^2 k_2$ [l·mol^{-1} s^{-1}]
3,4-Dihydro-2*H*-pyran	Methanol	0.38
	Ethanol	0.21
	Acetonitrile	0.70
Methyl *cis*-propenyl ether	Ethanol	0.93
	Acetonitrile	50
Methyl *trans*-propenyl ether	Ethanol	0.79
	Acetonitrile	41
Ethyl 1-isobutenyl ether	Methanol	33
	Ethanol	21
	Acetonitrile	63

As a result of kinetic control, tetracyanoethylene *(1)* and enol ethers in alcohol afford the acetal as trapping product and the 2+2-cycloadduct side by side. The relative rate constants of the reactions of the intermediate of type *(2)*, *i.e.* k_A [Alcohol]/$k_{Cycliz.}$, depend on the structure of the enol ether and of the alcohol; for the *cis*-form (*trans*-form) of methyl propenyl ether at 0 °C the following values of the ratio acetal/cyclobutane are found: in methanol 12.3 (2.3), in ethanol 5.3 (2.3), in 2-propanol 4.6 (1.4) and in *tert*-amyl alcohol 1.4 (0.59).

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[1] *R. Huisgen* and *G. Steiner*, J. Amer. Chem. Soc. *95*, 5054 (1973); cf. the experiments with *(1)* and *cis*-anethol: *P. D. Bartlett*, Quart. Rev. Chem. Soc. *24*, 473 (1970).

[2] *R. Huisgen* and *G. Steiner*, J. Amer. Chem. Soc. *95*, 5055 (1973).

[3] *G. Steiner* and *R. Huisgen*, J. Amer. Chem. Soc. *95*, 5056 (1973).

[4] *R. Huisgen* and *G. Steiner*, Tetrahedron Lett. *1973*, 3763.

[5] *G. Steiner* and *R. Huisgen*, Tetrahedron Lett. *1973*, 3769.

[6] *F. K. Fleischmann* and *H. Kelm*, Tetrahedron Lett. *1973*, 3773.

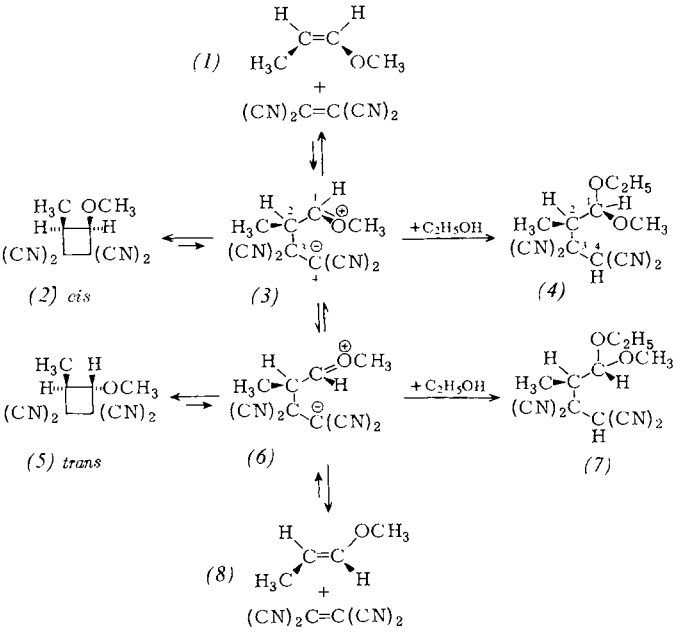
[7] *J. K. Williams*, *D. W. Wiley*, and *B. C. McKusick*, J. Amer. Chem. Soc. *84*, 2210 (1962).

[8] *K. Dimroth*, *C. Reichardt*, *T. Siepmann*, and *F. Bohlmann*, Liebigs Ann. Chem. *661*, 1 (1963); *C. Reichardt*: Lösungsmitteleffekte in der organischen Chemie. Verlag Chemie, Weinheim 1969.

[9] Replacements by piperidine in *p*-halonitrobenzenes: *H. Suhr*, Chem. Ber. *97*, 3277 (1964).

[10] Addition constants of secondary amines to acetylenecarboxylic esters: *B. Giese* and *R. Huisgen*, Tetrahedron Lett. *1967*, 1889.

(8), respectively, with tetracyanoethylene (TCNE)[1], leads to the acetals *(4)* and *(7)* which contain two chiral centers (C-1 and C-2). Surprisingly, the addition of ethanol occurs stereospecifically. With ethanol at 0 °C the *cis*-propenyl ether *(1)* gives 84% of the acetals *(4)* and *(7)*[1] in the ratio 18:1 together with 16% of the *cis*-cyclobutane *(2)* (Scheme 1). The reaction is complete in 15 min; NMR analysis identifies the products of the kinetically controlled reaction.



Scheme 1

On the other hand, the *trans*-propenyl ether *(8)* combines with TCNE in ethanol to give preferentially the acetal *(7)* [*(4)*:*(7)* = 1:17]; there is also formed 30% of the 2+2-cycloadducts, these being composed of 29% of the *trans*-cyclobutane *(5)* and ≈1% of the *cis*-isomer *(2)* (Scheme 1). The methyl and ethyl groups of the enol ether and the alcohol can be exchanged: now TCNE in methanol reacts with the ethyl *cis*-propenyl ether *(9)* to give the acetals *(4)* and *(7)* in the proportion 1:29, while the *trans*-enol ether *(10)* gives rise to *(4)* and *(7)* in a 13:1 ratio. Reaction of the *cis*-zwitterions of type *(3)* with alcohols is 5–8 times faster than the cyclization to *(2)*. This preference for formation of acetals rather than of cyclobutanes is less for the *trans*-zwitterions of type *(6)*, the ratios being 2.3 and 1.7, respectively (Table 1). If the zwitterions from the enol ethers *(1)* and *(8)* with TCNE were formed in random conformations, the stereospecificity should be small and the reaction in alcohol would be expected to afford the diastereoisomeric acetals *(4)* and *(7)* in approximately identical ratios. From the high stereospecificity of the acetal formation it must be concluded that most

Table 1. Reactions of alkyl *cis*- and *trans*-propenyl ethers with TCNE in alcohols and alcoholysis of the cyclobutanes.

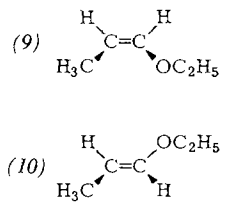
Reaction	*T* [°C]	Acetals [%] *(4)*	*(7)*	*(4)*:*(7)*	Cyclobutanes [%] *cis*	*trans*
(1) + TCNE in ethanol	0	79.6	4.4	18:1	16 *(2)*	< 1 *(5)*
(8) + TCNE in ethanol	0	4	66	1:17	≈ 1 *(2)*	29 *(5)*
(9) + TCNE in methanol	0	3	86	1:29	10 *(11)*	≈ 1 *(12)*
(10) + TCNE in methanol	0	58.6	4.4	13:1	< 1 *(11)*	37 *(12)*
(2) + ethanol	0	98	2	49:1		
(11) + methanol	25	1	99	1:99		
(12) + methanol	25	98	2	49:1		

Conformations of the Zwitterionic Intermediates from Tetracyanoethylene and Alkyl Propenyl Ethers

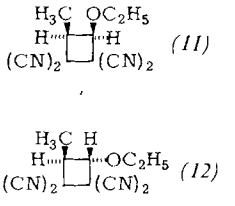
By *Rolf Huisgen*, *Reinhard Schug*, and *Gerd Steiner*[*]

The addition of ethanol to the zwitterions *(3)* and *(6)* that are formed from methyl *cis*- *(1)* and *trans*-propenyl ether

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(9)



(11)

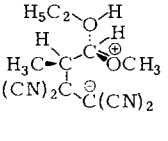
(10)

(12)

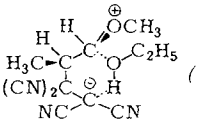
of the zwitterions arise in the 'U'-conformations *(3)* and *(6)*, *i.e.*, in the state where the Coulomb potential of the charge centers is lowest; a donor-acceptor interaction between the electrophilic and nucleophilic centers may contribute to the stabilization of the spatial arrangement.

In acetonitrile the zwitterions *(3)* and *(6)* undergo cyclization to *(2)* and *(5)* and *cis-trans*-isomerization by rotation in the proportions 1:5 and 1:4, respectively, which correspond to 16% and 20% of non-stereospecifically formed cyclobutanes[2].

The stereospecificity of acetal formation in alcohol is higher. Clearly a configuration-stabilizing interaction of the zwitterion and alcohol occurs at an early stage. The concurring 2+2-cycloaddition in alcohol is strikingly more stereospecific than the one in acetonitrile. In alcohol the ring closure to the cyclobutane has a chance only if the zwitterions are formed in the conformations *(3)* and *(6)* that are ideal for cyclization. Some "badly oriented" zwitterions, nevertheless, are formed and are trapped by the alcohol as shown by comparison with the 98—99% stereospecificity of acetal formation on ethanolysis of the pure methoxycyclobutane *(2)* and on methanolysis of the ethoxycyclobutanes *(11)* and *(12)* (Table 1). The comparatively slow ring opening of the cyclobutanes[1] produces almost wholly "ideal" zwitterions whose reaction with alcohol is highly stereospecific.



(13)



(14)

The configuration of the acetals *(4)* and *(7)* must be proved by X-ray structure analysis. As shown in Scheme 1 and in *(13)* we favor selective attack of the alcohol on the carbonium-oxonium center "from above" rather than reaction *via* the hydrogen bonded chelate *(14)* which should lead to compounds that are epimeric at C-1.

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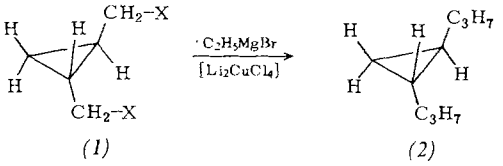
[1] For isolation and determination of structure of *(4)* and *(7)* see *R. Huisgen, R. Schug,* and *G. Steiner*, Angew. Chem. *86*, 47 (1974); Angew. Chem. internat. Edit. *13*, 80 (1974).

[2] *R. Huisgen* and *G. Steiner*, J. Amer. Chem. Soc. *95*, 5054, 5055 (1973).

Improved Carbon-Carbon Linking by Controlled Copper Catalysis[**]

By *Gerd Fouquet* and *Manfred Schlosser*[*]

During a search for the simplest and most effective pathway from 1-octanol to decane most of the conventional C—C linking reactions failed. Even a new variant[1] involving condensation of alkyl iodide with Grignard reagent in the presence of dilithium tetrachlorocuprate as catalyst produced yields which were hardly satisfactory (63% of decane) in view of our actual aim of preparing optically active dipropylcyclopropane *(2)*[2] starting from (*R,R*)-bis(hydroxymethyl)cyclopropane *(1)* (X=OH).

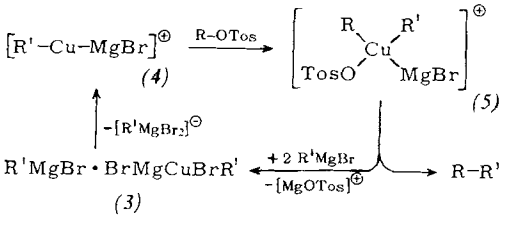


(1) *(2)*

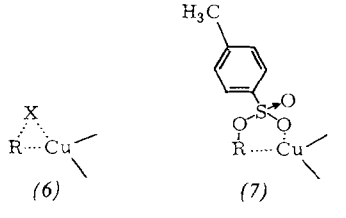
Our attempts to improve the method were guided by the following considerations:

1) Copper(I) compounds[3] prefer tetragonal coordination. Cuprates of the type $MCuXR$[4, 5] (M=MgX, Li, *etc.*; X=halide, alkoxide, or organic group) acquire the stable tetracoordination by self-association or by association with another organometallic species that may be present in excess. It is important that the mixed complex[6] expected in our case, *i.e. (3)*, be allowed to form without interference.

2) The role of initiator is assumed by the monomeric cuprate or the cation *(4)* derived therefrom which, as an electron-deficient compound, can undergo carbene-like (*(6)*) insertion into



a CX bond (*e.g.* to give *(5)*). Insertion should be facilitated by leaving groups which, like *p*-toluenesulfonates *(7)*, are capable of 1,4-interactions.



(6) *(7)*

As shown in Table 1, a "catalyst breeding" step (mixing of Grignard reagent and copper catalyst at −78 °C followed by gradual warming to room temperature, below which no condensation occurs) and use of *p*-toluenesulfonates instead of iodides or even bromides leads to a striking improvement. The Grignard component can be varied at will. In contrast, only primary *p*-toluenesulfonates react well, while secondary and tertiary ones give poor yields of product—if any—presumably owing to steric hindrance of insertion. The smooth reaction of *(1)* (X=OTos) to give *(2)* also confirms that no carbocationic, -radical, or -anionic intermediates are involved.

Surprisingly, it also proved possible to replace acetate groups[11] occupying allylic and benzylic positions by the hydrocarbon moiety of Grignard compounds, apparently because acetates can likewise exhibit a chelating action. Thus *trans*-crotyl acetate was converted regio- and stereoselectively into *trans*-2-octene *(8)* (88%).

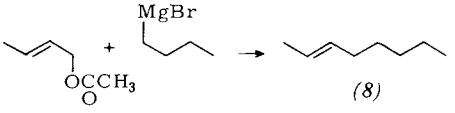
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[**] This work was supported by the Schweizerischer Nationalfonds (Project No. 2.593.71). Thanks are also due to BASF, Ludwigshafen, for supplying starting materials.

Table 1. Condensation reactions between *p*-toluenesulfonates (R—OTos) and Grignard compounds (R'—MgX).

R in R—OTos [a]	R' in R'—MgBr [b]	R—R' Yield [%] [c]
[d]	C_2H_5	79
C_2H_5	C_6H_{11}	98
C_2H_5	C_6H_5	90
C_8H_{17}	C_2H_5	98
C_8H_{17}	$(H_3C)_3C$	96
C_6H_5	C_2H_5	0
C_6H_5	C_6H_{11}	51
C_6H_5	$(H_3C)_3C$	0
C_6H_{11}	C_2H_5	3
$-(CH_2)_{12}-$	$(H_3C)_3C$	99

[a] OTs = $OSO_2-C_6H_4-CH_3$.
[b] Grignard reagent always added in excess (1.4 equiv.).
[c] Glc analyses; internal reference substance; calibration factors for peak area correction; standard deviation ±3%.
[d] *(1)*, X = OTos.



(8)

Similarly, *cis*-2-octene (50%) was obtained from *cis*-crotyl acetate.

2,2-Dimethyldecane:

Octyl *p*-toluenesulfonate (40 mmol) in tetrahydrofuran solution (50 ml) was treated at −78 °C with *tert*-butylmagnesium bromide (56 mmol in 32 ml of diethyl ether) and Li_2CuCl_4[1] (0.2 mmol in 2 ml of tetrahydrofuran)[7]. The reaction mixture was allowed to warm to room temperature during 2 h and stirring was continued for other 12 h. An aliquot sample was withdrawn and, after decane had been added as an internal standard, subjected to glc analysis. The main part of the reaction mixture was acidified with 2 N sulfuric acid, washed twice with water (2 × 50 ml), dried ($CaSO_4$), and evaporated. Distillation and rectification (b. p. 77—78 °C/15 torr) yielded 5.1 g (75%) of pure 2,2-dimethyldecane[8].

trans-2-Octene:

In the same manner *trans*-crotylacetate[9] (100 mmol), *n*-butylmagnesium bromide (140 mmol), and Li_2CuCl_4 (0.2 mmol) were mixed in a total volume of 50 ml of tetrahydrofuran and 40 ml of diethyl ether. A 62% yield of *trans*-2-octene[8, 9] (b. p. 120—122 °C) was isolated by spinning band column distillation; in addition 9% of 5-methyl-5-nonanol (b. p. 78 to 80 °C/2 torr) was obtained. According to glc (6 m 15% silicone rubber SE-30, 100 °C; 2 m 5% + 25% $AgNO_3$ + diethylene glycol, 30 °C) the yields amounted to 88% and 11%, respectively[10].

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[1] *M. Tamura* and *J. Kochi*, Synthesis *1971*, 303; see also *H. Gilman, R. G. Jones*, and *L. A. Woods*, J. Org. Chem. *17*, 1630 (1952).

[2] *M. Schlosser* and *G. Fouquet*, Synthesis *1972*, 200; Chem. Ber., in press.

[3] The catalytically active species appears to be a copper(I) derivative: CuI is as effective as Li_2CuCl_4.

[4] *H. Gilman, R. G. Jones*, and *L. A. Woods*, J. Org. Chem. *17*, 1630 (1952); *H. O. House, W. L. Respess*, and *G. M. Whitesides, ibid. 31*, 3128 (1966); *G. Wittig* and *G. Klar*, Liebigs Ann. Chem. *704*, 91 (1967); *E. J. Corey* and *G. H. Posner*, J. Amer. Chem. Soc. *89*, 3911 (1967); *90*, 5615 (1968); *G. H. Posner* and *C. E. Whitten*, Tetrahedron Lett. *1973*, 1815.

[5] Reviews: *J. F. Normant*, Synthesis *1972*, 63; see also: *W. Tochtermann*, Angew. Chem. *78*, 355 (1966); Angew. Chem. internat. Edit. *5*, 351 (1966); *G. Wittig*, Quart. Rev. Chem. Soc. *20*, 191 (1966); *G. H. Posner*, Org. React. *19*, 1 (1972).

[6] Review: *M. Schlosser*: Struktur und Reaktivität polarer Organometalle. Springer-Verlag, Heidelberg 1973, particularly pp. 11—16.

[7] Subsequent addition of the *p*-toluenesulfonate, *e.g.* after 3 h at 0 C, leads to the same result.

[8] Identity and purity were checked by elemental analyses, vpc, as well as mass, ^1H-, and ^{13}C-NMR and infrared spectra.

[9] Corrected for an impurity of 5% *cis* isomer present in the starting material.

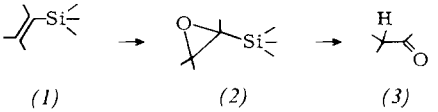
[10] Formation of this normal acetate reaction product may be even further reduced (< 5%) if larger amounts of CuI (*ca.* 1 equiv.) are used instead of Li_2CuCl_4.

[11] *Note added in proof:* Lithium dialkylcuprates can also undergo condensation reactions with *tertiary* allylacetates; however, they overwhelmingly involve attack at the vinylogous position and allylic shift of the double bond (*P. Rona, L. Tökes, J. Tremble*, and *P. Crabbé*, Chem. Commun. *1969*, 43; *R. J. Anderson, C. A. Henrik*, and *J. B. Siddall*, J. Amer. Chem. Soc. *92*, 735 (1970)).

Convenient Synthesis of Vinylsilanes and Their Use in Ketone Synthesis[**]

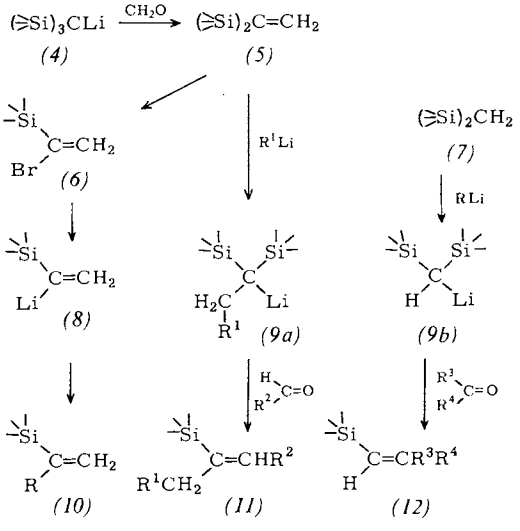
By *Bengt-Thomas Gröbel* and *Dieter Seebach*[*]

Vinylsilanes *(1)* can be converted into carbonyl derivatives *(3) via* epoxides *(2)*[1]. Thus all C—C coupling reactions in which vinylsilanes are formed represent potential methods for producing carbonyl compounds.



(1) *(2)* *(3)*

We now describe new α-silyllithium reagents *(8)* and *(9)* from which vinylsilanes *(10)*—*(12)* having different substitution patterns are accessible by simple C—C bond formation or by Peterson olefination.



Compound *(8)*[2] is produced from tris(trimethylsilyl)methyllithium *(4)*[3] which is first converted into the olefin *(5)*[4] in 70% yield by a Peterson reaction[5]. Compound *(5)* can be transformed into *(6)*[6], which is subjected to bromine-lithium exchange with *tert*-butyllithium[7]. The substituted reagents of type *(9a)* are prepared in more than 90% yield by addition[2a, 8] of alkyllithium compounds R^1Li to *(5)*. Solutions of reagent *(9b)*[3a] are also obtained in yields exceeding 90% by metalation of *(7)* in an improved process.

Compound *(8)* was subjected to the action of alkyl halide, aldehyde, or ketones, whereupon the products *(10)* were

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Table 1. Substitution patterns, yields, and a number of characteristic NMR data for the products *(10)*, *(11)*, and *(12)*. In all reactions the electrophile was added to a THF solution of the lithium reagent at −80 °C and the reaction mixture allowed to warm over 14 h. All the compounds gave correct elemental analyses.

Reaction	Electrophile			Yield [%] [a]	NMR [δ] silyl	olefinic H
(8) → *(10)*		R				
	n-pentyl iodide	*n*-C_5H_{11}		83	0.05	5.28, 5.50
	benzaldehyde	$C_6H_5CH(OH)$		64	−0.08	5.40, 5.68
	cyclohexanone	$(CH_2)_5C(OH)$		60	0.12	5.29, 5.56
	benzophenone	$(C_6H_5)_2C(OH)$		62	0	5.03, 5.53
(9a) → *(11)*		R^1	R^2			
	formaldehyde	*n*-C_4H_9	H	73	0.05	5.28, 5.50
	benzaldehyde	*n*-C_4H_9	C_6H_5	62	−0.08, 0.15	6.78, 7.2 [b]
	formaldehyde	*s*-C_4H_9	H	64	0.08	5.30, 5.44
	formaldehyde	*t*-C_4H_9	H	71	0.09	5.46, 5.57
	benzaldehyde	*t*-C_4H_9	C_6H_5	64	−0.08, 0.15	6.92, 7.18 [b]
	cinnamaldehyde	*t*-C_4H_9	$CH{=}CHC_6H_5$	60	0.13, 0.25	6.24—7.25 [b]
(9b) → *(12)*		R^3	R^4			
	benzaldehyde	C_6H_5	H	70 [c]	0.03, 0.17	5.79, 6.37, 6.85, 7.27 [b]
	cinnamaldehyde	$CH{=}CHC_6H_5$	H	35	0.15, 0.25	5.6—6.0, 6.4—7.0 [b]
	benzophenone	C_6H_5	C_6H_5	65	−0.12	6.19

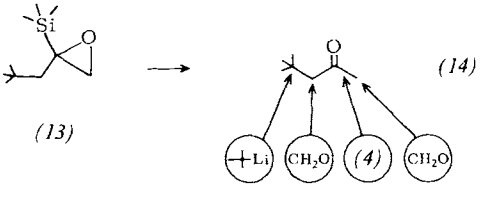
[a] Based on distilled products.

[b] As seen from the NMR spectra, *E*/*Z* isomeric olefins are formed, ratio 1:1.0—1:1.4.

[c] $n_D^{20} = 1.5230$ (*L. H. Sommer et al.*, J. Amer. Chem. Soc. *76*, 1613 (1954): 1.5270).

formed in 60—85% yield (see Table 1). Reaction of reagents *(9)* with nonenolizable carbonyl compounds proceeds *via* olefination to give good yields of the vinylsilanes *(11)* and *(12)* (see Table 1)[***].

As the first example of the production of a ketone from a vinylsilane we may cite the epoxidation of *(11)*, $R^1 = tert$-butyl, $R^2 = H$, to *(13)* and its hydrolysis to methyl neopentyl



(13) *(14)*

ketone *(14)*[9] in an overall yield of 74%. The origin of the individual C atoms of *(14)* is indicated below the formula. We thus have at our disposal a novel building-block system for the synthesis of ketones.

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[***] *Note added in proof:* Meanwhile *H. Sakurai et al.* (Tetrahedron Lett. *1973*, 4193) have published another route for preparation of *(9b)* giving two examples of its reaction with ketones.

[1] Only aldehydes have so far been synthesized by this route: *G. Stork* and *E. Colvin*, J. Amer. Chem. Soc. *93*, 2080 (1971).

[2] *(8)*, Mg instead of Li: see a) *A. G. Brook, J. M. Duff*, and *D. G. Anderson*, Can. J. Chem. *48*, 561 (1970); *(8)*, $(C_2H_5)_3Si$ instead of $(CH_3)_3Si$ and Mg instead of Li: see b) *G. Stork* and *B. Ganem*, J. Amer. Chem. Soc. *95*, 6152 (1973); *(8)*, $(C_6H_5)_3Si$ instead of $(CH_3)_3Si$: see [2a] and c) *A. G. Brook* and *J. M. Duff*, Can. J. Chem. *51*, 2024 (1973).

[3] a) *M. A. Cook, C. Eaborn, A. E. Jukes*, and *D. R. M. Walton*, J. Organometal. Chem. *24*, 529 (1970); b) *O. W. Steward, J. S. Johnson*, and *C. Eaborn*, *ibid. 46*, 97 (1972); c) *O. W. Steward* and *J. S. Johnson*, *ibid. 55*, 209 (1973).

[4] By reaction with an excess of paraformaldehyde. *(5)* has hitherto only been accessible by multi-step syntheses: *A. D. Petrov, V. F. Mironov*, and *V. G. Glukhovtsev*, Otdel. Khim. Nauk *1956*, 461; Chem. Abstr. *50*, 16663 i (1956); *G. Fritz* and *J. Grobe*, Z. Anorg. Allg. Chem. *309*, 77 (1961). Pivalaldehyde (80%), benzaldehyde (71%), cinnamaldehyde (51%), and butanal (43%) can also be olefinated by *(4)*.

[5] *D. J. Peterson*, J. Org. Chem. *33*, 780 (1968); *D. Seebach, M. Kolb*, and *B. Th. Gröbel*, Chem. Ber. *106*, 2277 (1973), and further literature cited therein; *C. Trindle, J.-T. Hwang*, and *F. A. Carey*, J. Org. Chem. *38*, 2664 (1973); *F. A. Carey* and *O. Hernandez*, *ibid. 38*, 2670 (1973).

[6] *G. Fritz* and *J. Grobe*, Z. Anorg. Allg. Chem. *309*, 99 (1961).

[7] *H. Neumann*, Diplomarbeit, Universität Giessen 1973.

[8] Addition of RLi to monosilylolefins, *e.g.*: *L. F. Cason* and *H. G. Brooks*, J. Amer. Chem. Soc. *74*, 4582 (1952); J. Org. Chem. *19*, 1278 (1954); *T. H. Chan, E. Chang*, and *E. Vinokur*, Tetrahedron Lett. *1970*, 1137.

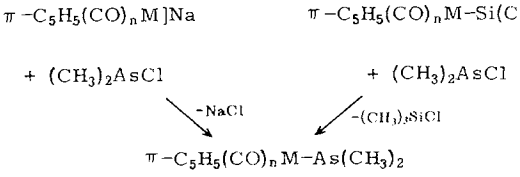
[9] Dinitrophenylhydrazone m.p. 99.3—100 °C [*F. C. Whitmore et al.*, J. Amer. Chem. Soc. *63*, 2035 (1941): m.p. 100 °C].

Dimethylarsenido-Transition Metal Complexes—Stable Organometallic Lewis Bases

By *Wolfgang Malisch* and *Max Kuhn*[*]

Complexes of the type $L_nM{-}AsR_2$ (M = transition metal, L = ligand; *n* = f(M)) are regarded as being capable of existence provided that electronegative substituents (R = CF_3, C_6F_5, Cl) reduce the donor strength of the As atom sufficiently to suppress association *via* ligand elimination producing doubly bridged dinuclear or polymeric polynuclear complexes $[L_{n-1}M{-}AsR_2]_x$[1, 2]. That only bridged complexes have so far been obtained in the case of compounds with R = CH_3[5], in spite of numerous attempted syntheses[3, 4], lends support to this concept.

We have now found that under certain conditions (25 °C, 12 h, nonpolar medium) mononuclear complexes of this type with M = Cr, Mo, W, and Fe can be prepared in good yields by use of the cyclopentadienylcarbonylmetalates and dimethylchloroarsane or by exchange reactions starting with the analogous trimethylsilyl compounds[6].



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These first representatives of monomeric dialkylarsenido-transition metal complexes prove to be unexpectedly stable. Thus they can be kept without decomposition in common organic solvents for a considerable time; in some cases decomposition can be induced only by heating the pure substances.

Hence in contrast to previous assumptions[1,4], the introduction of electropositive substituents does not necessarily render the system more labile for the increased basicity is compensated by an enhanced stability of the M—CO unit. In fact, both criteria seem to be of comparable importance in discussions of association processes involving CO elimination (compare ν_{CO} for corresponding C_6F_5 or CF_3 derivatives[1]).

A characteristic feature of the complexes *(1)—(4)* is their ready reaction (1) with various halides. This reactivity closely resembles that of trialkylarsanes but contrasts sharply with that of all R_2As-transition metal complexes so far known[1,2].

Table 1. Dimethylarsenido-transition metal complexes *(1)—(4)*.

π-$C_5H_5(CO)_nM$—$As(CH_3)_2$ [a]	M. p. [b] [°C]	IR [c] ν_{CO} [cm^{-1}]	^{1}H-NMR [d] $\delta_{C_5H_5}$ [Hz]	δCH_3 [Hz]
M = Cr; n = 3 *(1)*	36	1988	−223	−52
light orange needles		1927		
		1909		
M = Mo; n = 3 *(2)*	54—55	1993	−239	−49
yellow-brown needles		1922		
		1904		
M = W; n = 3 *(3)*	69—70	1995	−241	−57
light orange needles		1923		
		1906		
M = Fe; n = 2 *(4)*	—	1997	−208	−41
red liquid		1949		

[a] Analytical data in accordance with the formula given.
[b] Sealed capillary, Cu block.
[c] Cyclohexane solution.
[d] Benzene solution, TMS as external standard (60 MHz).

Quaternization of the metal-substituted arsanes opens up an excellent preparative route to cations having special ligand systems and is superior to conventional preparations of such species[7] because of its uniform reaction course.

Table 2. Quaternization reactions: reactants and products.

Complex	Quaternization agent	Product	ν_{CO} [a] [cm^{-1}]
(1)	CH_3I	$[Cp(CO)_3CrAs(CH_3)_3]I$	2037
			1982
			1957
(3)	$C_6H_5C(O)CH_2Br$	$[Cp(CO)_3WAs(CH_3)_2CH_2C(O)C_6H_5]Br$ [b]	2047
			1974
			1945
(2)	$(CH_3)_3SiCH_2Cl$	$[Cp(CO)_3MoAs(CH_3)_2CH_2Si(CH_3)_3]Cl$	2055
			1984
			1955
(3)	$(CH_3)_3SiI$	$[Cp(CO)_3WAs(CH_3)_2Si(CH_3)_3]I$	2044
			1972
			1944
(3)	HCl	$[Cp(CO)_3WAs(CH_3)_2H]Cl$ [c]	2043
			1970
			1939

[a] CsI cells; $CHCl_3$ solution (acetone for M = Cr).
[b] $\nu C(O)C_6H_5$: 1660 cm^{-1}.
[c] νAsH: 2023 cm^{-1}.

$$2\ \pi\text{-}C_5H_5(CO)_3M\text{-}As(CH_3)_2 \xrightarrow{100\,°C/1h} [\pi\text{-}C_5H_5(CO)_3M]_2 + (CH_3)_2As\text{-}As(CH_3)_2$$

$$\pi\text{-}C_5H_5(CO)_nM\text{-}As(CH_3)_2 \xrightarrow{+R\text{-}X,\ (1)} [\pi\text{-}C_5H_5(CO)_nMAs(CH_3)_2R]^{\oplus}X^{\ominus}$$

$$\pi\text{-}C_5H_5(CO)_nM\text{-}Si(CH_3)_3 \xrightarrow{+R\text{-}X,\ (2)} + (CH_3)_2AsCl + -(CH_3)_3SiCl \rightarrow [\pi\text{-}C_5H_5(CO)_nMAs(CH_3)_2R]^{\oplus}X^{\ominus}$$

The pale yellow, high melting salts, which are readily soluble in polar solvents, can generally be obtained directly *via* route (2) from the silyl complex without isolation of intermediates.

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[1] *W. R. Cullen* and *R. G. Hayter*, J. Amer. Chem. Soc. *86*, 1030 (1964); *M. Cooke, M. Green*, and *D. Kirckpatrick*, J. Chem. Soc. *A 1968*, 1507.

[2] *W. R. Cullen, D. J. Patmore*, and *J. R. Sams*, Inorg. Chem. *12*, 867 (1973).

[3] *E. W. Abel* and *G. V. Hutson*, Inorg. Nucl. Chem. *30*, 2339 (1968); *Y. L. Baay* and *A. G. MacDiarmid*, Inorg. Nucl. Chem. Lett. *3*, 159 (1967).

[4] *R. G. Hayter*, Inorg. Chem. *2*, 1031 (1963); J. Amer. Chem. Soc. *85*, 3120 (1963).

[5] *W. Ehrl* and *H. Vahrenkamp*, Chem. Ber. *106*, 2550, 2556 (1973).

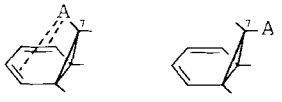
[6] *W. Malisch, H. Schmidbaur*, and *M. Kuhn*, Angew. Chem. *84*, 538 (1972); Angew. Chem. internat. Edit. *11*, 516 (1972); *W. Malisch, ibid. 85*, 228 (1973); *12*, 235 (1973).

[7] *R. J. Haines, R. S. Nyholm*, and *M. H. B. Stiddard*, J. Chem. Soc. *A 1967*, 94; *A. R. Manning, ibid. A 1967*, 1084.

Stereochemical Control by Secondary Through-Space Interaction: *exo/endo*-Stability of 7-Acceptor-Substituted 2,4-Norcaradienes[1]

By *Wolf-Dieter Stohrer* and *Jörg Daub*[*]

An acceptor (A) attached to C-7 of a norcaradiene can adopt an *exo* or an *endo* orientation. The *endo* arrangement *(1)* should permit a stabilizing through-space charge transfer directly from the antisymmetric highest occupied orbital of the diene to the antisymmetric acceptor orbital, in addition to the direct interaction between the Walsh orbital and the acceptor orbital[2]. A secondary interaction of this kind can be ruled out for the *exo* arrangement *(2)* and should therefore favor the *endo* over the *exo* arrangement.



(1) *(2)*

(a), A = CH_2^+

However, experiments show the *exo* form of 7-acceptor-substituted norcaradienes to be the more stable[3,4].

EH calculations[5] confirm this unexpected difference in stability: the *exo* cation *(2a)* is found in a model calculation to be 0.53 eV more stable than its *endo* isomer *(1a)* (the bisected arrangement is assumed for the cationic substituents), whereas the difference $\Delta E_{endo} - \Delta E_{exo}$ amounts to only 0.31 eV for the corresponding 7-methyl derivatives. Thus the lower stability of the *endo* cation cannot be ascribed solely to steric effects. The same qualitative EH results as for *(1a)* and *(2a)* are also obtained for other acceptor-substituted norcaradienes[6].

According to *Hoffmann*[2], the stabilizing influence of a C(7)-acceptor on norcaradienes arises from interaction between the occupied antisymmetric Walsh orbital of the three-membered ring and the unoccupied antisymmetric acceptor orbital. In norcaradiene, however, this Walsh orbital is not localized but mixes, as discussed in detail for the analogous case of semibullvalene[7], with the antisymmetric orbitals of the diene. In accord with the general rules, the occupied antisymmetric diene orbital and the occupied Walsh orbital undergo mixing to a bonding combination of lower energy and an antibonding one of higher energy.

Owing to the raised energy of the orbital and the high coefficient density at C(7) (cf. Fig. 1, center)[7], the latter combination is an even stronger donor than the Walsh orbital in an isolated cyclopropane[8] and is primarily responsible for the stabilizing interaction with the acceptor. This interaction is *a priori* (with the coefficient at C-7) of equal magnitude for the *endo* and the *exo* form (Fig. 1, left-hand side and right-hand side, respectively). The sign of the acceptor orbital in the *endo* and *exo* form is fixed since the primary interaction with the coefficient at C-7 is bonding in character, *i.e.* the coefficients on C-7 and on the acceptor necessarily have the same sign. Therefore, contrary to initial expectations, the additional secondary through-space interaction between the diene and the acceptor is not bonding, but *antibonding*, in nature (Fig. 1, left-hand side) and thus destabilizing. This destabilization, which is clearly apparent from the calculated orbital energies, is absent in the *exo* form (Fig. 1, right-hand side) thus accounting for its higher stability[9].

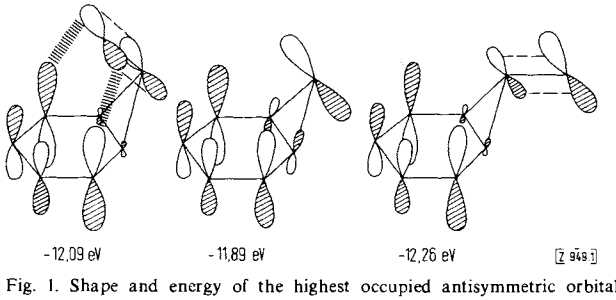


Fig. 1. Shape and energy of the highest occupied antisymmetric orbital in 2,4-norcaradiene (center) and in CH_2^+-substituted norcaradiene in the *endo* (left-hand side) and *exo* form (right-hand side).

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[1] Presented in part at the Chemiedozententagung Münster on March 27, 1973, Abstr. p. 14.

[2] *R. Hoffmann*, Tetrahedron Lett. *1970*, 2907; *H. Günther, ibid. 1970*, 5173.

[3] *J. Daub* and *W. Betz*, Tetrahedron Lett. *1972*, 3451.

[4] *P. Warner* and *Shih-Lai-Lu*, J. Amer. Chem. Soc. *95*, 5099 (1973).

[5] *R. Hoffmann*, J. Chem. Phys. *39*, 1397 (1963); *40*, 2745 (1964).

[6] *W.-D. Stohrer* and *J. Daub*, unpublished.

[7] *R. Hoffmann* and *W.-D. Stohrer*, J. Amer. Chem. Soc. *93*, 6941 (1971).

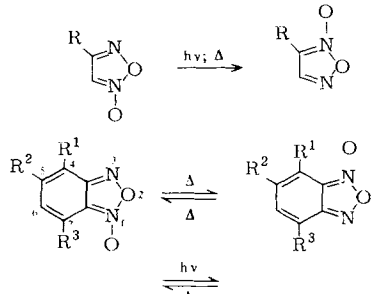
[8] This is confirmed by EH calculations; the formation of the *exo* cation *(2a)* is favored by 0.31 eV compared with the formation of the "isolated" cyclopropylmethyl cation.

[9] *Loew* and *Wilcox* have reached the same conclusion, adopting somewhat different but essentially equivalent reasoning. *L. M. Loew* and *C. F. Wilcox*, personal communication.

Photochromism of 4-Substituted Benzofuroxans[**]

By *Gion Calzaferri, Rolf Gleiter, Karl-Heinz Knauer, Hans-Dieter Martin*, and *Erika Schmidt*[*]

Benzofuroxans are an interesting class of compounds from both a preparative and a theoretical point of view. Whereas



	(1)	*(2)*	*(3)*	*(4)*	*(5)*	*(6)*
R^1	NO_2	NO_2	NO_2	Br	Br	Cl
R^2	H	Cl	H	OCH_3	H	H
R^3	Cl	H	H	H	Br	Cl

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furoxans undergo both thermal and photochemical isomerization (*e.g. (1)*)[1] the analogous isomerization (2) of benzofuroxans has so far only been detected as a thermally induced process[2].

In the present communication we shall show that (2) can also be photochemically induced.

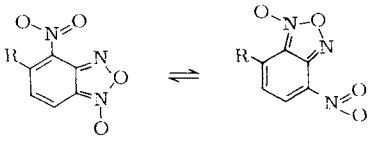
With this aim in mind we studied 4-substituted benzofuroxans since for these derivatives the thermal equilibrium (2) is shifted largely to the left-hand side for stereochemical reasons (R > H)[2] and the isomers exhibit different electronic spectra. Conventional flash spectroscopy[3] was employed to detect a photoreaction (2') since half-life times of $\tau_{1/2} \leqslant 10^{-1}$ s were to be expected for the thermal reverse reaction (2')[2,4].

On irradiation of ethanolic solutions of the benzofuroxans *(1)* to *(4)* in a flash apparatus a short-lived transient (half life (25 C) $10^{-2} - 5 \times 10^{-4}$ s) was observed in each case which underwent thermal reversion to the starting compound. The reaction was found to be of first order and independent of the oxygen concentration of the solution. At low temperature (−150 C) the photochemical intermediate was sufficiently stable for recording an electronic spectrum.

The ^{1}H-NMR spectrum of an irradiated solution of *(1)* in $(CD_3)_2CO$ could also be recorded at −80 °C. Apart from the AB spectrum of protons H-5 and H-6 ($\delta_A = 8.76$, $\delta_B = 7.81$ ppm; $J = 8$ Hz) of the starting material, a new AB spectrum ($\delta_A = 8.38$, $\delta_B = 8.00$ ppm; $J = 8$ Hz) was detected.

The electronic spectra recorded prior to and after irradiation are very similar with respect to the positions and intensities of the bands. Hence we conclude from this observation and from the pronounced reversibility of the thermal reverse reaction that the transient is an isomer of the starting compound and rule out previously discussed[2,4] alternatives to the furoxan structure.

Two isomerization reactions can be considered for *(1)* to *(3)*: 1) a photoreaction according to (2') or 2) a Boulton-Katritzky rearrangement[2] (3).



(3)

The second reaction type can be ruled out as a photoisomerization on the basis of the following findings: According to eq. (3) reaction of *(1)* should yield *(2)* and reaction of *(2)* should afford *(1)*. However, the electronic spectra of the two transients *(1a)* and *(2a)*, respectively, differ from those of *(1)* and *(2)*. Moreover, these rearrangements (*(1)* → *(2)* and *(2)* → *(1)*) should proceed irreversibly in the flash experiment since the solutions of *(1)* and *(2)* are stable under the experimental conditions. No irreversible reaction is observed. Eq. (3) would predict that *(3)* yields an identical product on irradiation, which is certainly not the case.

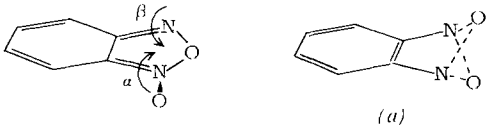
The following facts indicate isomerization according to eq. (2'): A comparison of the activation parameters listed in Table 1 for the thermal reverse reaction of the transients *(1a)* → *(1)*, *(2a)* → *(2)*, *(3a)* → *(3)*, *(4a)* → *(4)* with those from the thermal isomerization[2,4] of *(5)* and *(6)* shows good agreement. In contrast, an activation energy of > 20 kcal/mol was estimated for isomerization of *(3)* according to eq. (3)[5].

On irradiation of *(1)* the signal of the proton H-5 in the NMR spectrum is shifted upfield by 0.38 ppm, and that of the proton H-6 downfield by 0.19 ppm. Similar shifts in the same directions have been reported for isomerizations according to (2)[4,5].

Our results indicate that benzofuroxans isomerize according to eq. (2') on irradiation. This reaction permits synthesis of benzofuroxans displaying strong steric hindrance in position 7 and the study of their properties.

The isomerization of benzofuroxans according to eq. (2) has been postulated to involve dinitrosobenzene[2,4] but no unequivocal proof has yet been forthcoming.

Brief irradiation of benzofuroxans at −40 °C effects no change in the optical density in the spectrum; the lifetime of any possible intermediate must therefore be $< 10^{-4}$ s at this temperature.



(a)

Model CNDO/2 calculations performed on the isomerization (2)[6] revealed a disrotatory but nonsynchronous motion of the two oxygen atoms for the minimum energy pathway[7]. Transition states are found at $\alpha = 90$, $\beta = 0$ and $\alpha = 180$, $\beta = 90°$[8]. Between these values a local minimum *(a)* occurs at $\alpha = 135$ and $\beta = 22.5°$ (0.5 eV more stable than the transition states). It remains to be established whether this minimum is merely an artifact of the calculation method.

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[1] *A. R. Gagneux* and *R. Meier*, Helv. Chim. Acta *53*, 1883 (1970); *J. Ackrell* and *A. J. Boulton*, J. C. S. Perkin I *1973*, 351.

[2] *A. J. Boulton* and *P. B. Ghosh*, Advan. Heterocycl. Chem. *10*, 1 (1969); and literature cited therein.

[3] *G. Porter*, Techn. Org. Chem. *3*, 1055 (1963).

[4] *G. Englert*, Z. Elektrochem. *65*, 854 (1961); *F. B. Mallory*, *S. L. Manatt*, and *C. S. Wood*, J. Amer. Chem. Soc. *87*, 5433 (1965).

[5] *R. K. Harris*, *A. R. Katritzky*, *S. Øksne*, *A. S. Bailey*, and *W. G. Paterson*, J. Chem. Soc. *1963*, 197.

Table 1. Kinetic data for the thermal reverse reaction of the transient according to eq. (1).

Compound	Solvent	Temp. [C]	k [s^{-1}]	E_a [kcal/mol]	$\Delta G^{\neq}$ [kcal/mol]	$\Delta S^{\neq}$ [cal/mol·°K]
(1)	ethanol	25	64.3	16.7	15.0	3.7
(2)	ethanol	25	66.1	17.1	15.0	5.2
(3)	ethanol	25	1.43×10^3	13.4	13.2	−1.2
	chloroform	25	6.76×10^2	15.6	13.6	4.8
(4)	ethanol	25	4.68×10^2	14.8	13.8	1.3
	chloroform	25	1.73×10^2	17.7	14.2	9.6
(5) [a]	acetone	30	1.7×10^2	16.3	14.6	4
(6) [a]	acetone	30	2.2×10^2	16.5	14.5	5

[a] Data from ref. [4], determined by NMR spectroscopy.

[6] *J. A. Pople, D. P. Santry*, and *G. A. Segal*, J. Chem. Phys. *43*, 129 (1965); *J. A. Pople* and *D. L. Beveridge*: Approximate Molecular Orbital Theory. McGraw-Hill, New York 1970.

[7] The geometry of the furoxan model was chosen such that on rotation of α and β by 180 an identical molecule is obtained. The ONO angle was assumed to be 146 52', the N—O distance to be 1.40 Å, the C—N distance to be 1.30 Å, and the C—C distance to be 1.40 Å. A variation of the angles α and β should describe the reaction coordinate to a first approximation.

[8] *R. Hoffmann, R. Gleiter*, and *F. B. Mallory*, J. Amer. Chem. Soc. *92*, 1460 (1970).

Tri-*tert*-butylstannylamine and Tri-*tert*-butylstannyl-*N*-deuterioamine: The First Primary Stannylamines

By *Hans-Jürgen Götze*[*]

Whereas the primary amines R_3SiNH_2 ($R=CH_3$, C_2H_5)[1] and R_3GeNH_2 ($R=C_6H_5$)[2] have been known for some time, attempts to prepare a homologous stannylamine R_3SnNH_2 *(1)* have hitherto been unsuccessful. Reaction of trialkyltin halides[3] or trialkylphenyltin[4] (alkyl = CH_3, C_2H_5, C_3H_7, i-C_3H_7, i-C_4H_9, neopentyl, and C_6H_{11}) in liquid NH_3 with KNH_2 or $LiNH_2$ invariably leads to the secondary *(2)* or tertiary stannylamines *(3)*, the primary amines *(1)* which probably represent the initial reaction product undergoing condensation with elimination of ammonia.

$$R_3SnX + NH_3 \xrightarrow[-HX]{(+KNH_2)} R_3SnNH_2 \qquad (1)$$

$$2\,(1) \xrightarrow{-NH_3} (R_3Sn)_2NH \qquad (2) \qquad \text{or} \qquad 3\,(1) \xrightarrow{-2\,NH_3} (R_3Sn)_3N \qquad (3)$$

X = Halogen, C_6H_5;
(2), R = C_3H_7, i-C_3H_7, i-C_4H_9, neopentyl, C_6H_{11}
(3), R = CH_3, C_2H_5, C_3H_7

However, the corresponding reaction of tri-*tert*-butylphenyltin with KNH_2 at 0 °C has now been found to constitute the first preparation of tri-*tert*-butylstannylamine *(1a)*.

$$[(CH_3)_3C]_3SnC_6H_5 + NH_3 \xrightarrow[-C_6H_6]{(+KNH_2)} [(CH_3)_3C]_3SnNH_2 \qquad (1a)$$

No by-products such as *(2)* or *(3)* were observed. Evidently the bulky *tert*-butyl group hinders condensation of *(1a)*. Tri-*tert*-butylstannyl-*N*-deuterioamine *(1b)* could also be prepared in a similar manner with KND_2 in ND_3.

The primary stannylamines *(1a)* and *(1b)* are colorless liquids which are rapidly hydrolyzed to tri-*tert*-butyltin hydroxide and small amounts of hexa-*tert*-butyldistannoxane even by traces of moisture; at 100 °C hydrolysis proceeds quantitatively to give the distannoxane. Both compounds react with CO_2 to give bis(tri-*tert*-butylstannyl) carbonate *(4)* if the reaction is accompanied by hydrolysis.

$$2\,(1a) \xrightarrow[-2\,NH_3]{+H_2O,\,+CO_2} [(t\text{-}Bu)_3SnO]_2CO \qquad (4)$$

In contrast to the behavior of other stannylamines[5] the Sn—N bond in *(1a)* and *(1b)* is not cleaved by CCl_4.

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The composition and structure of compounds *(1a)* and *(1b)* were established by elemental analysis, molecular-weight determination, and by mass and vibrational spectroscopy (Table 1). The mass spectrum of *(1a)* (selection): *m/e* (relative intensity) = 250 (5.8%) $(C_4H_9)_2SnNH_2$, 194 (3.6%) $C_4H_9(H)SnNH_2$, 177 (4.5%) C_4H_9Sn; 136 (8.4%) $SnNH_2$, 120 (1.6%) Sn. Only the fragments corresponding to ^{120}Sn are given. The molecular ion of $(C_4H_9)_3SnNH_2$ (*m/e* 307) was not observed.

Table 1. IR and Raman data for the primary stannylamines *(1a)* and *(1b)* in cm^{-1} [a,b].

	$(t\text{-Bu})_3SnNH_2$		$(t\text{-Bu})_3SnND_2$	
	IR	Raman	IR	Raman
$\nu_{as}NH_2(D_2)$	3380 w	3385 vw (dp?)	2479 w	2482 vw (dp?)
$\nu_s NH_2(D_2)$	3326 w	3327 s (p)	2433 w	2436 w (p)
$\delta NH_2(D_2)$	1573 m	—	1118 m	—
νSn—N	564 m	567 m (p)	527 s	530 w (sh)

[a] IR spectra: Perkin-Elmer grating spectrometer Model 325.
[b] Raman spectra: Cary 82 (Varian).

Experimental:

All operations should be carried out with rigorous exclusion of moisture and CO_2 (argon atmosphere): A solution of $(t\text{-Bu})_3C_6H_5Sn$[6] (4.25 g, 0.012 mol) in diethyl ether (30 ml) is allowed to react in a two-limbed pressure apparatus[4] with KNH_2 (2.0 g, 0.036 mol) in liquid NH_3 (50 ml) at 0 °C. The mixture is frequently shaken throughout the reaction (*ca.* 24 h). After evaporation of NH_3 and ether, vacuum distillation of the crude product affords *(1a)* as a colorless liquid, b. p. 53—54 °C/0.15 torr; yield 2.2 g (62%). Compound *(1b)* can be prepared analogously with KND_2 in ND_3: b. p. 60 to 61 °C/0.2 torr.

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[1] *H. Bürger*, Inorg. Nucl. Chem. Lett. *1*, 11 (1965); *N. Wiberg* and *W. Uhlenbrock*, Chem. Ber. *104*, 2643 (1971).

[2] *C. A. Kraus* and *C. B. Wooster*, J. Amer. Chem. Soc. *52*, 372 (1930).

[3] *K. Sisido* and *S. Kozima*, J. Org. Chem. *29*, 907 (1964); *R. E. Highsmith* and *H. H. Sisler*, Inorg. Chem. *8*, 996 (1969).

[4] *O. Schmitz-DuMont, H.-J. Götze*, and *H. Götze*, Z. Anorg. Allg. Chem. *366*, 180 (1969); *H.-J. Götze*, J. Organometal. Chem. *47*, C 25 (1973).

[5] *A. Marchand, C. Lemerle*, and *M.-T. Forel*, J. Organometal. Chem. *42*, 353 (1972).

[6] *H.-J. Götze*, Chem. Ber. *105*, 1775 (1972).

Rapid Procedure for Liquid-Phase Peptide Synthesis: The Crystallization Method

By *Manfred Mutter* and *Ernst Bayer*[*]

Polyethylene glycols are particularly suitable as solubilizing C-terminal protecting groups in peptide synthesis in homogeneous solution[1-3]. Hitherto, lower-molecular reagents and coupling components have been separated from the peptide chain growing on the polyethylene glycol by means of diafiltration[1,2], so that a single synthetic cycle including change of solvent required about a day. The synthesis can be accelerated by crystallization of the polymeric peptide at each stage. Polyethylene glycol differs from other solvents such as polyvinyl alcohol used in the liquid-phase method by its marked

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[**] Times required for the two syntheses: 7 and 10 days, respectively, including isolation and purification.

tendency to crystallization and formation of a stable helical structure[4–6]. So long as this conformation and the tendency to crystallize is retained as the peptide sequence grows on the polyethylene glycol, purification could be effected by crystallization at each stage and the synthetic cycle would be shortened to 1—2 hours.

X-ray investigation has now shown that the same reflections are given by the free polyethylene glycols (*e.g.* PEG 15000) and the polyethylene glycol peptide esters (*e.g.* the octapeptide BOC-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met) when these are precipitated in crystalline form from diethyl ether by methylene chloride ($d_1 = 3.81$ Å; $d_2 = 4.643$ Å).

The ability to crystallize avoids the possibility of inclusions, such as occur with gelatinous precipitates[7], and the excess of protected amino acid used can be removed quantitatively.

Figure 1 shows the principles of the synthesis together with the times required for individual operations.

acid/1.2 N HCl) and the polymeric peptide is again precipitated by ether, washed, and dried.

By this method we have synthesized, *inter alia*, the difficult partial sequence 14—20 of ACTH H-Gly-Lys-Lys-Arg-Arg-Pro-Val-OH and the biologically active peptide "Substance P"[8–10] in short times, using PEG of molecular weight 6000 and 15000, respectively[**]. This rapid procedure for liquid-phase synthesis retains the previous advantages of the method, and the operations have been simplified to the extent that coupling with an amino acid group is effected in a shorter time than in the solid-phase method and, further, the synthesis can be automated.

Polyethylene glycols having molecular weights in the range 20000 to 2000 are suitable for the crystallization procedure, and capacities of 0.1 mmol/g to 1 mmol/g of polymer can be achieved.

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(A) $PEG{-}OH + HOOC{-}CHR{-}NH{-}BOC \xrightarrow[2.\ H^{\oplus}]{1.\ CDI,\ DCCI} PEG{-}OCO{-}CHR{-}NH_3^{\oplus}X^{\ominus}$

(B) Separate activation of the *N*-protected amino acid by DCCI [11] and filtration of the DC-urea or use of active esters

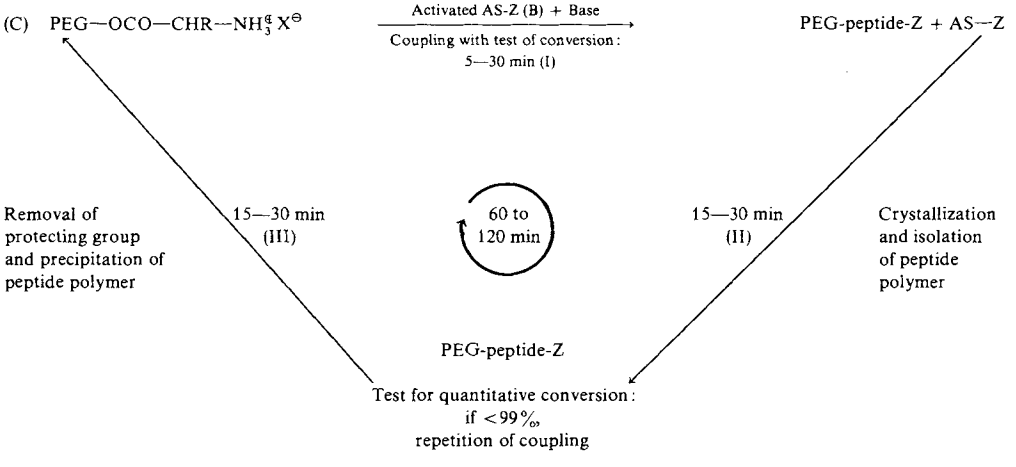


Fig. 1. Synthetic cycle of the crystallization procedure of the liquid-phase method. Abbreviations: PEG = polyethylene glycol; AS = amino acid; CDI = 1,1'-carbonyldiimidazole; others according to [12].

Synthesis cycle: 1,1'-Carbonyldiimidazole or DCCI is used for esterification (A) of the first C-terminal amino acid with polyethylene glycol[1, 2]. A 10% solution of the polymeric peptide in CH_2Cl_2 is treated at 0 °C with the activated derivative of the next amino acid (B) in 1.5—3-fold excess while the tertiary base needed to neutralize the free amino group is simultaneously added dropwise. After 5 min the degree of conversion is tested on aliquot portions of the mixture (C). When coupling is complete (max. time 30 min) the solution is concentrated (20%) and ether is added to it with vigorous stirring until the polymeric peptide is quantitatively precipitated (100—200 ml of ether per 20—30 ml of CH_2Cl_2). The peptide polymer is filtered off (glass frit), washed twice with diethyl ether, and dried. At this stage the quantitative removal of the excess reagents can be tested by the simple procedure of thin-layer chromatography (R_F of the peptide polymer = 0). Then the protecting group is removed (*e.g.* by glacial acetic

[1] *M. Mutter, H. Hagenmaier*, and *E. Bayer*, Angew. Chem. *83*, 883 (1971); Angew. Chem. internat. Edit. *10*, 811 (1971).

[2] *E. Bayer* and *M. Mutter*, Nature *237*, 512 (1972).

[3] Nachr. Chem. Techn. *20*, 495 (1972).

[4] Polyglycol Catalog, Farbwerke Hoechst AG, Frankfurt.

[5] *H. Tadokoro, Y. Chatani, T. Yoshihara, S. Tahara*, and *S. Murahashi*, Makromol. Chem. *73*, 109 (1964).

[6] *R. Springer* and *R. Lang*, Deut. Apoth.-Ztg. *108*, 1605 (1968).

[7] *M. M. Shemyakin, Y. A. Ovchinnikov, A. A. Kiriushkin*, and *I. V. Kozhevnikova*, Tetrahedron Lett. *1965*, 2323.

[8] *K. Vogler, W. Haefely, A. Hürlimann, R. O. Studer, W. Lergier, R. Strässle*, and *K. H. Bemeis*, Ann. N. Y. Acad. Sci. *104*, 378 (1963).

[9] *R. O. Studer et al.*, to be published.

[10] *E. Bayer* and *M. Mutter*, Chem. Ber., in press.

[11] *H. Hagenmaier* and *H. Frank*, Hoppe-Seylers Z. Physiol. Chem. *353*, 1973 (1972).

[12] IUPAC Recommendations, Eur. J. Biochem. *1*, 375 (1965).

Correlation of the ^{13}C-NMR Chemical Shifts of Carbonyl and Thiocarbonyl Groups[**]

By *Hans-Otto Kalinowski* and *Horst Kessler*[*]

Empirical correlations between structural parameters and spectral data are of use both to the practical spectroscopist as well as the theoretician. The linear relationship found by us between the chemical shifts of ^{13}C=O- and ^{13}C=S-groups enables one to predict the value of these shifts to within a few ppm (cf. Table 1).

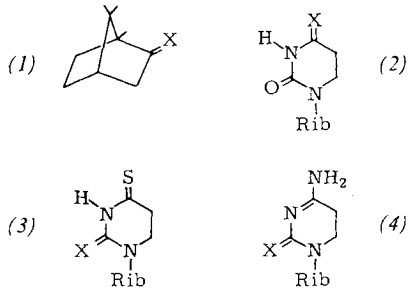


Table 1. δ(^{13}C) Data for carbonyl and thiocarbonyl compounds.

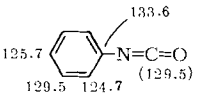
Compound X = O, S	Solvent	$\delta_{C=O}$	$\delta_{C=S}$	$\delta_{C=S}$ calc. [a]	$\Delta\delta_{O,S}$ obs.	Ref.
X=C=X		124.2	192.8	—	68.6	[2]
(1)	CCl_4	215.6 [b]	269.0	266.0	53.4	[3]
RR'C=X						
R = R' = *p*-CH_3O—C_6H_4	$CDCl_3$	194.2	233.3	235.0	39.1	
R = R' = *p*-$(CH_3)_2N$—C_6H_4	$CDCl_3$	193.0	230.6	233.3	37.6	
R = R' = $N(CH_3)_2$	$CDCl_3$	165.7	194.0	193.7	28.3	
R = R' = $NHCH_3$	$CDCl_3$	160.5	182.7	186.1	22.2	
R = CH_3, R' = NH_2	—	172.7	207.2	203.9	34.5	[4]
R = CH_3, R' = NHC_6H_5	—	169.5	200.4	199.2	30.9	[4]
R = Cl, R' = $N(CH_3)_2$	$CDCl_3$	149.5	175.1	170.0	25.6	
R = H, R' = $N(CH_3)_2$	$CDCl_3$	162.4	188.1	188.9	25.7	
R,R' = CH_3—N—$(CH_2)_2$—N—CH_3	$CDCl_3$	161.3	182.9	187.3	21.6	
R,R' = CH_3—N—$(CH_2)_3$—N—CH_3	$CDCl_3$	156.7	179.6	180.7	22.9	
R—N=C=X						
R = CH_3		121.4	128.6	129.4	7.2	[4]
R = C_2H_5		122.5	130.7	130.9	8.2	[4]
R = C_6H_5	$CDCl_3$	125.2	135.7	135.0	10.5	
R = c-C_6H_{11}		123.6	132.3	132.6	8.7	[4]
(2)	DMSO	164.9 [c]	191.3 [c]	192.5	26.4	[5]
(3)	DMSO	144.3 [c]	174.0 [c]	169.9	29.7	[5]
(4)	DMSO	157.1 [c]	181.1 [c]	181.2	24.0	[5]

[a] Calculated according to eq. (1).
[b] Original value recalculated with $\delta^{TMS} = 193.4 + \delta^{CS_2}$.
[c] Original value recalculated with $\delta^{TMS} = 128.7 + \delta^{C_6H_6}$.

The chemical shifts listed in Table 1 can be reproduced by eq. (1) (correlation coefficient $r = 0.997$)[11]:

$$\delta_{C=S} = 1.45\,\delta_{C=O} - 46.5\ \text{ppm} \qquad (1)$$

The utility of this equation can be readily illustrated using phenylisocyanate as example. The following assignments have been made for the signals of the different carbon atoms in this compound[4, 6]:



Thus, the signal of the C=O groups should coincide with the signals of the C-3 and C-5 atoms. However, the chemical shift calculated from the value for phenylisothiocyanate using eq. (1) is 125.0 ppm. The off-resonance spectrum, on the other hand, shows quite clearly that the CO signal is overlapped, not by the signals of C-3 and C-5, but by those of C-2, C-6, and C-4 ($\delta_{C=O} = 125.2$ ppm)[11].

Equation (1) can also be used in the investigation of tautomeric equilibria: In the case of acetic acid—thioacetic acid (178.1 and 194.5 ppm, resp.) the deviation from the calculated value for $CH_3C(S)OH$ (211.9 ppm) can—in agreement with other spectroscopic studies[8]—be considered as indicative of the thioacetic acid being present in the thiol form.

It can be seen from Table 1 that the difference between the chemical shifts found for ^{13}C=O and ^{13}C=S ($\Delta\delta_{O,S}$) decreases with increasing donor action of the substituents. In principle, this also applies for the difference[7] between the n,π* energies of C=O- and C=S-compounds. Unfortunately, however, there are too few unequivocally assigned n,π* transitions available as yet to make such a correlation possible.

The chemical shifts of ^{13}C are essentially determined by the paramagnetic shielding[9] [eq. (2)].

$$\sigma_p = -\frac{\text{const}}{\Delta E}\left(\frac{1}{r^3}\right)_{2p}[Q_{AA} + \Sigma Q_{AB}] = -\frac{A}{\Delta E} \qquad (2)$$

r = average radius of the 2p orbital of carbon
Q_{AA}, Q_{AB} = charge density and bond order terms
A = collection of all terms excepting ΔE
ΔE = mean excitation energy of all occupied orbitals.

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Alteration of the lowest excitation energy (HOMO→LUMO n,π* for the C=X group) could have the largest influence on σ_p. For substituted benzophenones and thiobenzophenones the following correlation has been derived:

$$\Delta(n,\pi^*)/\Delta(n,\pi^*)^O = 1.54^{[10]}$$

Assuming that the agreement of this correlation with that of eq. (1) is not incidental, then, for eq. 2, we may write:

$$\frac{\Delta\sigma_p^O}{\Delta\sigma_p^S} = \frac{\Delta A^O \Delta\Delta E^S}{\Delta A^S \Delta\Delta E^O} = \frac{\Delta(n,\pi^*)^S}{\Delta(n,\pi^*)^O} \quad (3)$$

Furthermore, if it is assumed that the energy of the n,π* transition approximates to ΔE and the diamagnetic influence on the ^{13}C chemical shift can be ignored, eq. (4) should be valid, *i.e.* all the terms in eq. (2) except ΔE change in the same direction or not at all in the transition from carbonyl to the corresponding thiocarbonyl compounds. We are at present carrying out MO calculations to test this prediction.

$$\Delta A^O/\Delta A^S = 1 \quad (4)$$

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[1] The values for CO_2 and CS_2 have not been used in the correlation, since they contain *two* oxygen and sulfur atoms respectively, and CO_2 was measured in the gas phase.

[2] *R. Ettinger, P. Blume, A. Patterson,* and *P. C. Lauterbur,* J. Chem. Phys. *33*, 1597 (1960).

[3] *P. V. Demarco, D. Dodrell,* and *E. Wenkert,* Chem. Commun. *1969*, 1418.

[4] *G. C. Levy* and *G. L. Nelson:* Carbon-13 Nuclear Magnetic Resonance. Wiley Interscience, New York 1972.

[5] *A. J. Jones, D. M. Grant, M. W. Winkley,* and *R. K. Robins,* J. Amer. Chem. Soc. *92*, 4079 (1970).

[6] *L. F. Johnson* and *W. C. Jankowski:* Carbon-13 NMR Spectra. Wiley Interscience, New York 1972.

[7] A direct relationship between ^{13}C chemical shift and n,π* excitation cannot be assumed, since variation in structure influences both factors in different ways. The parameters were kept constant by comparing C=X compounds of similar structure.

[8] *M. J. Janssen* in *S. Patai:* The Chemistry of Carboxylic Acids and Esters. Interscience, London 1969, p. 705.

[9] *J. A. Pople,* Mol. Phys. *7*, 301 (1963); *M. Karplus* and *J. A. Pople,* J. Chem. Phys. *38*, 2803 (1963).

[10] *D. S. Blackwell, C. C. Liao, R. O. Loutfy, P. de Mayo,* and *S. Paszy,* Mol. Photochem. *4*, 171 (1971).

[11] Note added in proof (December 7, 1973): The assignment of all ^{13}C signals is also confirmed by the coupled ^{13}C spectrum.

Selenium Oxide Tetrafluoride

By *Konrad Seppelt*[*]

The search for the unknown selenium oxide tetrafluoride ($SeOF_4$) has now lasted almost thirty years[1]. Since the discovery of pentafluoroorthoselenic acid $HOSeF_5$[2] the general concensus of opinion was that $SeOF_4$ might be very unstable. Thus $SeOF_4$ was not detectable in the vacuum pyrolysis of the potassium salt $KOSeF_5$[3].

However, it has now proved possible to synthesize $SeOF_4$ using pure sodium pentafluoroorthoselenate[4] as starting material.

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Selenium oxide tetrafluoride can be trapped as a white solid at 196°C. It decomposes above −100°C with liquifaction and frothing to give a colorless viscous liquid, which, according

$$NaOSeF_5 \xrightarrow{200°C/10^{-3}\,Torr} NaF + SeOF_4$$

to its NMR spectrum, is a mixture of several substances. The mass spectrum (75eV) of $SeOF_4$ shows the ions $SeOF_4^+$ (*m/e*=172, 14%), $SeOF_3^+$ (153, 100%), SeF_3^+ (137, 53%), $SeOF_2^{2+}$ (134, 89%), SeF_2^{2+} (118, 27%), $SeOF^+$ (115, 97%), SeF^+ (99, 29%), SeO^+ (96, 20%), and Se^+ (80, 35%). The only impurity found is $SeO_2F_2^{2+}$ (150, 57%).

Like its sulfur analog SOF_4, $SeOF_4$ very probably has a trigonal bipyramidal structure.



The fluorine atoms can rapidly interchange position. Accordingly, only one singlet is observed in the ^{19}F-NMR spectrum at δ = −88.7 ppm (solution in CF_3Cl, −110°C, $CFCl_3$ as external standard; 56.4 MHz). Remarkably, $SeOF_4$ has an absorption in common with SOF_4 at very low field strength (δ = −88.4 ppm[5]). The absence of the ^{77}Se isotope signals is a clear indication of the mobility of the fluorine atoms. Thus, isotope signals are observable in the case of the rigid molecules SeF_6, SeO_2F_2, and $SeOF_2$[6] but not in the case of SeF_4[7].

In the solid-state Raman spectrum [(−180°C, cm^{-1}) 1013 m, 755 m, 712 s, 608 m, 427 m, 387 w, 234 m] the band at 1013 cm^{-1} can be assigned to νSeO. This is the highest frequency so far recorded for a selenium-oxygen stretching vibration—for comparison, $SeOF_2$: 1005 cm^{-1}[8]—and would suggest the presence of a real double bond. Unequivocal assignment of the remaining bands is impossible without polarization and IR measurements.

It follows from the existence of the compounds $SeOF_4$ and $HOSeF_5$ that the chemistry of selenium is much more diverse than the chemistry of sulfur or tellurium; in the case of the latter elements only SOF_4 and $HOTeF_5$ have so far been found. This diversity is all the more surprising since selenium(VI) compounds are generally less stable than their sulfur and tellurium homologs. Finally, selenium oxide tetrafluoride is the only known compound of hexavalent selenium with fivefold coordination. The unusual coordination number also explains the instability of $SeOF_4$: the high viscosity of the "decomposition products" is indicative of polymerization. The previously reported decomposition[3] into SeF_6 and SeO_2F_2 could not be confirmed.

Received: September 21, 1973 [Z 952a IE]
German version: Angew. Chem. *86*, 103 (1974)

[1] *W. Hückel,* Nachr. Akad. Wiss. Göttingen, Math.-Phys. Kl. *1946*, 36.

[2] *K. Seppelt,* Angew. Chem. *84*, 212 (1972); Angew. Chem. internat. Edit. *11*, 630 (1972).

[3] *K. Seppelt,* Chem. Ber. *105*, 2431 (1972).

[4] *K. Seppelt,* Z. Anorg. Allg. Chem., in press.

[5] *F. B. Dudley, J. N. Shoolery,* and *G. H. Cady,* J. Amer. Chem. Soc. *78*, 568 (1956).

[6] *T. Birchall, R. J. Gillespie,* and *S. L. Vekris,* Can. J. Chem. *43*, 1672 (1965).

[7] *E. L. Muetterties* and *W. D. Phillips,* J. Amer. Chem. Soc. *81*, 1084 (1959).

[8] *R. Paetzold,* Z. Chem. *4*, 272 (1964).

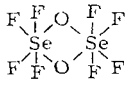
Diselenium Dioxide Octafluoride and Ditellurium Dioxide Octafluoride

By *Konrad Seppelt*[*]

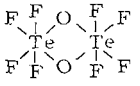
Selenium oxide tetrafluoride was recently detected as an unstable molecule that polymerizes above $-100\,^{\circ}C$[1]. From the polymerizate a homogeneous fraction can be separated which, considering its high volatility, can only be the oligomeric $(SeOF_4)_2$ or $(SeOF_4)_3$. Vapor density measurements (Mol. wt.: obs. 343.8, calc. 341.9) and the mass spectrum [75 eV; *m/e* 325 ($Se_2O_2F_7^+$ 0.6%), 172 ($SeOF_4^+$ 19%), 153 ($SeOF_3^+$ 100%), 137 (SeF_3^+ 26%), 134 ($SeOF_2^+$ 7%), 118 (SeF_2^+ 7%), 115 ($SeOF^+$ 15%)] favor the dimer *(1)*.

$$2SeOF_4 \xrightarrow{-100\,^{\circ}C} (SeOF_4)_2$$

The structure of a molecule with this empirical formula must contain a four-membered ring:



(1)



(2)

This structure is supported by the ^{19}F-NMR spectrum, which contains a highly resolved A_2B_2 pattern ($\delta_A = -55.5$, $\delta_B = -93.3$ ppm; $J_{AB} = 228$, $J_{^{77}Se_A} = 1398$, $J_{^{77}Se_B} = 1306$ Hz; $CFCl_3$ as external standard). Accordingly, each half of the molecule contains two fluorine atoms in the four-membered ring plane as well as one above and one below the plane.

A center of symmetry in the molecule should be observable in the vibrational spectra. In fact only one, presumably accidental, coincidence is observed, despite the large number of IR and Raman bands [IR, gaseous (cm^{-1}): 760 vs, 732 vs, 705 m, 670 w, 627 m, 559 w, 497 m, 431 m, 407 s, 352 m, and 268 w.—Raman, liquid (cm^{-1}): 774 m p, 722 vs p, 651 sh p, 647 s p, 634 w dp, 620 w dp, 472 s p, 430 m dp, 425 sh dp, 314 w dp, 288 s p, 254 sh dp, 249 s p, 194 w dp, 162 m p, 150 sh dp, 102 s p].

No $TeOF_4$ could be detected in the vacuum pyrolysis of lithium pentafluoroorthotellurate[2]; however, the colorless ditellurium dioxide octafluoride *(2)* (b. p. 77.5 °C, m. p. 28 °C) analogous to *(1)* is formed.

$$LiOTeF_5 \xrightarrow{200\,^{\circ}C/10^{-3}\,Torr} LiF + \{TeOF_4\} \downarrow (TeOF_4)_2 \quad (2)$$

Proof of structure once again follows from a molecular weight determination (obs. 429.7, calc. 439.2), the mass spectrum [75 eV; *m/e* 444 ($Te_2O_2F_8^+$ 18%), 425 ($Te_2O_2F_7^+$ 54%), 409 ($Te_2OF_7^+$ 37%), 222 ($TeOF_4^+$ 5%), 203 ($TeOF_3^+$ 34%), 187 (TeF_3^+ 100%), 168 (TeF_2^+ 17%), 165 ($TeOF^+$ 15%), 149 (TeF^+ 10%)], the ^{19}F-NMR spectrum (A_2B_2 type; $\delta_A = 53.5$, $\delta_B = 25.6$ ppm; $J_{AB} = 188.5$, $J_{^{125}Te_A} = 3700$, $J_{^{125}Te_B} = 3600$ Hz), and the vibration spectra [IR (cm^{-1}): 736 s, 719 vs, 698 s, 660 m, 641 s, 635 m, 405 s, 330 s, 308 s, 285 m, and 269 s.—Raman (cm^{-1}): 749 m p, 710 w dp, 680 vs p, 656 s p, 606 w p, 589 s dp, 357 m p, 336 m dp, 236 s p, 192 s p, 145 w p].

The stability of *(1)* towards hydrolysis is a sign of good steric shielding of the selenium by its octahedral surroundings. On the other hand, *(2)* is sensitive to hydrolysis. *(2)* reacts especially rapidly with fluoride donors such as KF with formation of higher polymers $(TeOF_4)_n$.

The ring structure discussed here for oxide fluorides is unusual, and, in our opinion, novel. Similar structures have previously only been observed in ions, *e.g.* $I_2O_{10}H_2^{4-}$[3] and $As_2O_2F_8^{2-}$[4]. The dimerization of $SeOF_4$ and of the hypothetical $TeOF_4$ with coordinative saturation (to the octahedron) shows how unfavorable fivefold coordination is and how even a four-membered ring system, despite the strained valence angles, constitutes a preferred structure for the molecules. The *cis* structure in the $O_2SeF_4(O_2TeF_4)$ system, which is also found in $(F_5SO)_2SF_4$[5], can only be explained electronically, since the *trans* structure leads to a sterically unhindered configuration. The distance between the two Se and Te atoms in *(1)* and *(2)*, respectively, is about 30% smaller than van der Waals distances would allow; on the other hand, it is only about 20% greater than a chalcogen-chalcogen single bond. This estimation was based on the most plausible angle at the oxygen (100°). An interchalcogen interaction (Se ··· Se or Te ··· Te) would appear highly improbable due to a lack of available electrons.

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[**] Thanks are due Dr. *R. Geist* for recording the mass spectra.

[1] *K. Seppelt*, Angew. Chem. *86*, 103 (1974); Angew. Chem. internat. Edit. *13*, 91 (1974).

[2] *K. Seppelt*, Z. Anorg. Allg. Chem., in press.

[3] *H. Siebert* and *H. Wegener*, Angew. Chem. 77, 507 (1965); Angew. Chem. internat. Edit. *4*, 523 (1965).

[4] *H. Dunken* and *W. Haase*, Z. Chem. *3*, 433 (1963); *4*, 156, 193 (1964).

[5] *C. I. Merril* and *G. H. Cady*, J. Amer. Chem. Soc. *85*, 909 (1963).

Reviews

Abstracts of selected progress reports and review articles

Use of lasers in the separation of isotopes is described by *C. B. Moore*. A species in a mixture of isotopes can be selectively excited by lasers. Numerous possibilities have been discussed for separation of the excited atoms or molecules, *e.g.* spontaneous predissociation, isomerization, or very fast reactions. Photopredissociation has functioned well in the only experimental separation of cited and nonexcited species to have been performed so far. A 1:1 mixture of CD_2O and CH_2O afforded D_2 and H_2 in a ratio of 1:6 (alongside 5% of HD). [The Application of Lasers to Isotope Separations. Accounts Chem. Res. *6*, 323—328 (1973); 31 references]

[Rd 686 IE—L]

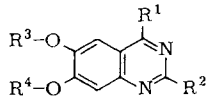
The photochemistry of aliphatic azo compounds in solution is the subject of a review by *P. S. Engel* and *C. Steel*. On UV irradiation one of three unimolecular reactions occurs: nitrogen elimination, *cis-trans* isomerization, or rearrangement to a hydrazone. The authors consider, *inter alia*, spectroscopy and triplet energies, as well as photosensitization. [Photochemistry of Aliphatic Azo Compounds in Solution. Accounts Chem. Res. *6*, 275—281 (1973); 69 references]

[Rd 687 IE—L]

Patents

Abstracts of selected "Deutsche Offenlegungsschriften" (DOS), *i.e.* provisionally published specifications as filed with the German Patent Office

1-Aryl-2-phenyl-1-(2-pyridyl)alkanols *(1)* and their acid-addition salts have an antihypercholesterolemic action together with good tolerance characteristics. They also exhibit estro-



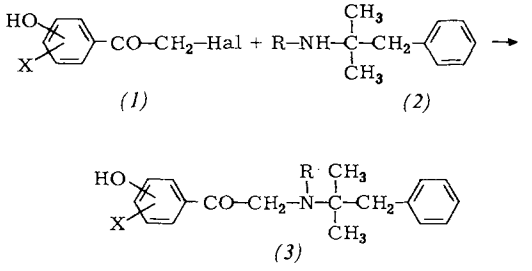
(1)

R = alkyl (C_1—C_5); X, X' = H, F, Cl, CF_3, OH, benzyloxy, alkyl, alkoxy, acyloxy (C_1 to C_4)

genic, ovary-stimulating, progestative, and contraceptive activities. [DOS 2111365; Merck Patent GmbH, Darmstadt]

[PR 113 IE –N]

Phenolic amino ketones *(3)* have a strong antiedemic action, which is probably due to stimulation of the adrenergic β receptors. The amino ketones *(3)* can be obtained by condensation of the halo ketones *(1)* with the amines *(2)* (X = H, OH;

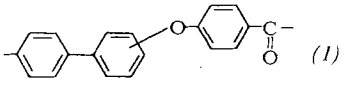


(1) *(2)* *(3)*

R = H, alkyl (C_1—C_3)). [DOS 2110545; Troponwerke Dinklage & Co., Köln-Mülheim]

[PR 114 IE –N]

Polyketones with favorable processing properties and having repeat units *(1)* are prepared by polymerization of the corresponding acyl chlorides with BF_3 in HF or in HF/SO_2. The acyl chlorides are obtained by Ullmann condensation of the hydroxybiphenyls with 4-chlorotoluene, oxidation of the intermediates to the carboxylic acids, and reaction of these with thionyl chloride. The polymerization proceeds within several hours at room temperature. Acylatable aromatic compounds

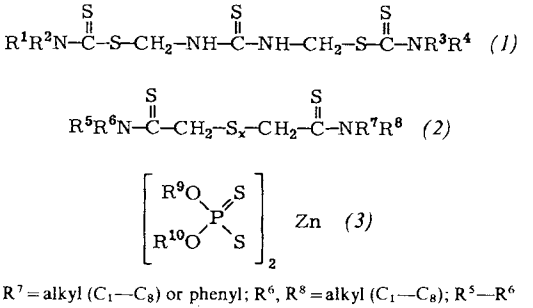


(1)

such as biphenyl, diphenyl ether, 4-phenoxybenzophenone, and 4,4'-diphenoxybenzophenone are added to adjust the chain length to the desired value. The new polyketones have high softening points, good stress cracking resistance to solvents, and relatively high elongations at break. They are therefore particularly suitable for the heat-resistant insulation of electric conductors, which can be twisted without danger of cracking the insulation. [DOS 2206836; Raychem Corp., Menlo Park]

[PR 121 IE—S]

A mixed accelerator for the vulcanization of EPDM elastomers consists of a) 25—75 wt.% of a thiourea *(1)* and b) 75—25 wt.% of a compound containing sulfur. Suitable compounds containing sulfur are: 1, polysulfides *(2)*; 2, tetramethylthiuram disulfide alone or mixed with bis(3-oxapentamethylene)thiuram disulfide; 3, zinc salts *(3)*; and 4, zinc salts of a product obtained from H_2NCH_2—CH_2OH, CH_2O, and



(1) *(2)* *(3)*

R^1—R^4, R^5, R^7 = alkyl (C_1—C_8) or phenyl; R^6, R^8 = alkyl (C_1—C_8); R^5—R^6 and R^7—R^8 form a piperidine, pyrrolidine, or morpholine ring with the N atom; R^9, R^{10} = alkyl residues (C_1—C_8), x = 2—6.

CS_2. The use of the mixture avoids undesirable sweating out on the surface of the vulcanized product. [DOS 2206648; Pennwalt Corp., Philadelphia, Pa.]

[PR 99 IE –E]

An improved method for the production of esters of phosphoric acid involves reaction of phosphorus halides *(1)* with (thio)-phenols *(2)* in the presence of a carbamate catalyst at temperatures of up to 250 °C. The N atom of the carbamate should form a complex with the P atom of *(1)*; examples of suitable carbamates are ethyl carbamate, ethyl *N*-phenylcarbamate, ammonium carbamate, and silver dithiocarbamate. High yields are obtained without contamination of the phosphoric acid esters with by-products. Monosubstitution, disubstitution, or trisubstitution of *(1)* can be achieved by the choice of temperature. The reaction of $POCl_3$ with cresol in the presence of ethyl carbamate, for example, leads at 105—110 °C to cresyl dichlorophosphate. Addition of phenol and heating to 135—150 °C leads to cresyl phenyl chlorophosphate, which is converted into cresyl diphenyl phosphate with further phenol at 200—210 °C. [DOS 2230912; Monsanto Co., St. Louis]

R_mPZ_n *(1)* Aryl-XH *(2)*

X = O, S; R = (cyclo)alkyl, (cyclo)alkenyl, (cyclo)alkynyl, aryl heterocycle, aryl-X, alkyl-X; $n = 1—3$; $m = 0—2$; $n+m = 3$; Z = Cl, Br.

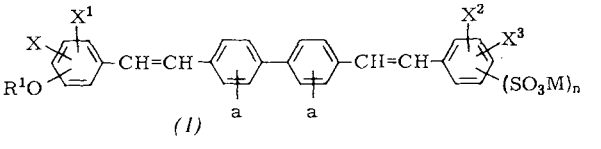
[PR 125 IE—V]

To prepare organic compounds containing labeled atoms, starting compounds, at least one of which contains a labeled atom, are brought into contact with fiber structures containing an enclosed enzyme that catalyzes the synthesis of the desired compound. Fiber-forming polymers of this type include cellulose esters, polyolefins, (co)polymers of acrylonitrile, (meth)acrylates, vinyl chloride, styrene, or polyamides. The enzyme reagents, which are made insoluble by the enclosure, can be easily recovered and reused. For example, [β-^{14}C]-L-tryptophan is obtained from [β-^{14}C]-DL-serine with an enzyme obtained from *E. coli* cells and enclosed in cellulose triacetate. Deuterium-labeled reduced nicotinamide adenine dinucleotide can be synthesized stereospecifically from NAD^+ and [1,1-D_2]-ethanol with alcohol dehydrogenase enclosed in cellulose triacetate. [DOS 2225797; Snam Progetti S.p.A., Milan] [PR 128 IE—V]

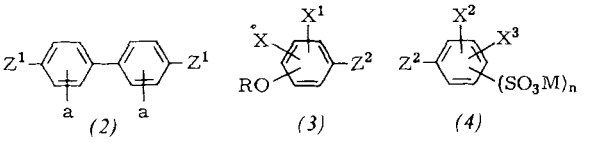
Transparent candle material that retains its transparency during storage, does not darken or discolor, and burns uniformly, consists of a thermoplastic polyamide resin and a combustible solvent that can dissolve the polyamide resin below about 100 °C to form a transparent gel. Unsaturated fatty acids and fatty alcohols, among other substances, are used as solvents. For optimum properties, the candle material should contain 5 to 35 wt.% of the polyamide resin. [DOS 2210220; Avon Products, Inc., New York] [PR 129 IE—E]

Magnetic data supports in which the magnetizable particles are incorporated directly in the support material so that the tape forms a homogeneous mass are produced from polypropylenes with molecular weights of 100000 to 5 million and containing 15 to 30 wt.% of material that is soluble in boiling heptane. In addition to polypropylene, copolymers of propylene with ethylene, vinyl acetate, and (meth)acrylic esters and mixtures of polypropylene with ethylene/propylene or ethylene/vinyl acetate copolymers may also be used. The polymers mentioned have good pigment tolerance and outstanding mechanical properties. The polymer is generally loaded with magnetic pigment in a weight ratio of 40:60 to 15:85. [DOS 2116760, Badische Anilin & Soda-Fabrik, Ludwigshafen] [PR 130 IE—E]

Bis-stilbene compounds such as *(1)* are used as optical brighteners for organic materials; detergents may contain 0.01—2 wt.% of at least one of these compounds *(1)*. They are prepared by reaction of equivalent quantities of *(2)*—*(4)* in the presence of a strongly basic alkali metal compound and a preferably hydrophilic, strongly polar solvent [DOS 2209221; Ciba-Geigy AG, Basel]



(1)



(2) *(3)* *(4)*

R^1 = alkyl (C_5—C_{18}), substituted alkyl (C_2—C_{20}), alkenyl (C_5,C_4)
X = H, alkoxy (C_1—C_4), halogen, alkenyl (C_3, C_4), alkyl (C_1—C_4)
X^1 = H, halogen, alkenyl (C_3,C_4), alkyl (C_1—C_4)
a = H, halogen, alkyl (C_1—C_4), alkoxy (C_1—C_4)
M = H, alkali metal, alkaline earth metal, NH_4, NHR_3^2
n = 1, 2
X^2,X^3 = H, halogen, alkyl (C_1—C_4), alkoxy (C_1—C_4)
Z^1,Z^2: one is CHO, the other $-CH_2P(O)(OR)_2$, $-CH_2P(O)(OR)R$, $-CH_2P(O)R_2$ or $-CH=PR_3$
R = substituted alkyl, aryl, cycloalkyl or aralkyl residue

[PR 148 IE—J]

BOOK REVIEWS

Wörterbuch der Chemie und der chemischen Verfahrenstechnik. Dictionary of Chemistry and Chemical Engineering. Vol. 2, English/German. By *L. De Vries* and *H. Kolb*. Verlag Chemie GmbH, Weinheim/Bergstr. and Academic Press, New York—London 1972. 1st ed viii 644 pp., bound DM 135.—.

The English-German edition of this technical dictionary now takes its place alongside the German-English edition, which appeared in 1970[*]. It consists of the actual dictionary section and an appendix containing a table of the chemical elements, a list of British and American weights and measures, and a temperature conversion table, as well as the abbreviations used. The terms listed (about 67000 entries) cover the vocabulary of pure and applied chemistry, particularly process

[*] Cf. Angew. Chem. internat. Edit. *10*, 947 (1971).

engineering, reactor technology, and the metal, petroleum, rubber, and textile industries, as well as the adjoining fields of physics, biology, medicine, mathematics, mineralogy, and crystallography and the disciplines of biochemistry, biophysics, atomic physics, *etc.*

In addition to the technical terms, the clearly legible and carefully prepared book (the number of printing errors found was negligible) also lists a large number of substances with their trivial names and systematic names. Some of the shortcomings found in the German-English edition have been eliminated in the present English-German edition. On leafing through the book, it was noted that the nomenclature rules were not strictly followed in some cases. For example, the German for manganous sulphate is Mangan(II)-sulfat, not Manganosulfat, while manganese fluosilicate is Manganfluorosilicat and not Mangansilicatfluorid. The translation of esters of hypophosphorous acid is also incorrect. These errors ought to be corrected in the next edition.

Nevertheless, the dictionary is a valuable aid to scientists and engineers, and a mine of information for technical translators.

Christian Weiske [NB 174 IE]

Laboratory Methods in Infrared Spectroscopy. Edited by *R. G. J. Miller* and *B. C. Stace*. Heyden & Son Ltd., London—New York—Rheine. 2nd ed., 1972, xi, 375 pp., numerous figures and tables, bound DM 56.50

IR spectroscopy has become a dependable workhorse for many problems of structural elucidation, identification, and quantitative analysis. The special strengths of IR spectroscopy are that it can be used for the investigation of substances in any aggregation state and that analyses can be carried out on samples in the microgram range and under extreme conditions. The present book may be very helpful in problems of this type that lie close to the limits of the range of application.

The editors have been able to bring together the experience of many practical workers in a manner that is rarely found in publications. The book, which contains numerous figures, diagrams, tables, and spectra, will undoubtedly prove useful in many IR laboratories.

Bernhard Schrader [NB 178 IE]

Physik griffbereit. Definitionen—Gesetze—Theorien (Physics at Your Fingertips. Definitions—Laws—Theories). By *B. M. Jaworski* and *A. A. Detlaf*. Friedr. Vieweg & Sohn, Braunschweig 1972. 1st ed., 892 pp., 259 figs., 26 tables, bound DM 24.80.

According to the foreword by the translator and German editor *F. Cap*, the present book is intended as a concise reference work for preparation for examinations and lectures and to provide "the internationally usual minimum of general and 'theoretical' physics that is to be expected of any physicist".

In agreement with this aim, the selection of material covers a wide range and is not to be found in the hitherto known German-language literature. The opening chapter on the fundamentals of classical mechanics includes basic concepts such as velocity and acceleration and the principal points of analytical mechanics, *i.e.* Lagrangian and Hamiltonian functions, as well as the variation principle. Hydromechanics and aeromechanics have a chapter to themselves. A chapter on thermodynamics contains both the classical theory and the principal concepts of the statistical approach. Two chapters on electricity and mangetism and on waves include the subject matter of normal lectures in electrodynamics and optics. In addition to the central points such as the Maxwell equations, the special theory of relativity, and geometric and wave optics, marginal fields such as acoustics, thermoelectric phenomena, and luminescence are also touched upon. The last chapter is devoted to advanced experimental physics and contains the fundamentals of atomic, nuclear, and elementary particle physics.

With this range of subject matter the book is well able to fulfill its authors' aims over wide areas. The smooth transition between the material of introductory theoretical lecturers and that of special experimental courses should help the student to form links between areas that are often treated as quite isolated from one another in Germany.

The selection of material is perhaps open to criticism with respect to solid-state physics. Many concepts crop up only as items scattered throughout the book, so that one cannot speak of a didactically systematic treatment of the subject. Important concepts such as Brillouin zone and *Umklapp* process are missing.

Some readers will notice a lack of up-to-dateness in the chapter on atomic physics, since recent developments as important as optical pumping and laser physics are omitted.

The most serious omission, however, is undoubtedly the absence of any bibliography at the ends of the various chapters. Reference to at least a few suitable text books for further reading would greatly enhance the value of the book.

On the whole, the book can be recommended to anyone who is less concerned with experimental facts than with having at hand a quick reference to fundamental theories.

R. Tilgner [NB 163 IE]

Annual Reports in Synthesis—1971. Eds. *J. McMurry* and *R. B. Miller*. Academic Press, New York—London 1972. 1st edn., xiv, 347 pp., $ 7.50.

This report, which is in its second year, is one more attempt to save the synthetic organic chemist from drowning in the continuously increasing deluge of information. Its eight chapters (C—C Bonding, Oxidations, Reductions, Heterocyclic Syntheses, Protecting Groups, Useful Preparative Methods, Various Reviews, and 'Completely Different Reactions') present the facts in the briefest form—reference, reaction equation and sometimes yield—and cover 49 primary journals of organic chemistry for the period between March 1st 1971 and March 1st 1972. As in the comparable collection of references in 'Reactiones Organicae' of the journal Synthesis, the series aims primarily at presenting the information in rapidly assimilable visual form.

To provide an idea of the completeness of this "box of cards in book form" its entries were compared with the short communications on synthetic methods that appeared during the above period in Angewandte Chemie and the Journal of the American Chemical Society. Very few gaps were noticeable. The rare mistakes that the Reviewer noted (*e.g.* pp. 120, 138, 168) were misprints. Although, to save time and expense, no index is provided, the information sought can generally be rapidly found through the detailed List of Contents. Longer thumbing through the book is rewarded by discovery of one or more methods new to the reader.

As the series is a considerable help in the study of the literature our first wish is for continuation of the series, but this can be coupled with a request for more cross-references in future volumes. This aid to the literature should, in the well-worn phrase, be to every chemist's hand and it is to be hoped that this will in fact occur in view of the extraordinarily cheap price of about one cent per reference.

Henning Hopf [NB 172 IE]

Synthetic Nucleotides. Vol. 1. By *G. R. Pettit*. Van Nostrand Reinhold Comp., New York—London 1972. 1st ed., viii, 252 pp., bound £ 10.00.

In this book, *G. R. Pettit* presents a long-needed comprehensive tabular survey of synthetic nucleotides.

All the important nucleotides mentioned from 1945 to June 1971, together with their methods of synthesis, are discussed in nine chapters, starting with the mononucleotides having the bases U, C, T, A, and G and their derivatives and proceding *via* the oligonucleotides to the polynucleotides. In each chapter the tables are preceded by brief descriptions and formulas for well-planned and well-proven syntheses.

In addition to the literature references, each table contains a brief outline of the phosphorylation method and information about the solvent and the chromatographic procedure. UV values, melting point, and yield are given. The tables also show whether R_f values, electrophoresis values, and elemental analyses are given in the original literature for the characterization of the nucleotides and what spectroscopic methods and enzymatic tests have been used.

The author has put a great deal of work into separating the wheat from the chaff in the nucleotide chemistry literature of the past 25 years, some of which is rather obscure. It is pleasing to know that the author intends to continue this work in the same way as his "Synthetic Peptides". It should be pointed out, however, that the present book has a number of shortcomings, both with regard to its content and of a technical nature.

In a book that claims complete coverage of the results of the last 25 years, the number of references (barely 350) is far too small. Furthermore, a good 10% of these are connected with the historical discussion in the introductory chapter. The author rightly criticizes the fact that the characterization of the nucleotides is often based on faith. It is therefore difficult to understand why he does not cite articles in which abundant use is made of enzymatic and spectroscopic techniques. Moreover, the table should also give experimental values from other publications. Another desirable feature would have been references to other recent important reviews.

Despite these reservations, the book should certainly be very useful to nucleotide chemists and to chemists who wish an insight into this field. It should find a place in any library.

Kay Schattka [NB 176 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal.

The Scientific Principles of Crop Protection. By *H. Martin*. Edward Arnold, London 1973 6. Edit., VIII, 423 p., bound £ 12.—.

Contents: Plant Resistance; External Factors; Biological Control; Pesticides; Measurement and Mechanics of Toxicity; Fungicides; Insecticides; Herbicides; Fumigants; Seed Treatment; Soil Treatment; Traps; Centres and Vectors of Infection.

Analytical Chemistry of Neptunium. By *V. A. Mikhailov*. From the series "Analytical Chemistry of the Elements". Edited by *A. P. Vinogradov*. Israel Program For Scientific Translation, Jerusalem–London/Halsted Press, New York 1973. VII, 235 pp., bound £ 9.35.

Contents: Separating Neptunium from Foreign Elements; Quantitative Determination of Neptunium.

Coordination Chemistry – XIV. Edited by the International Union of Pure and Applied Chemistry in collaboration with the National Research Council of Canada and the Chemical Institute of Canada. Symposium Editor: *A.B.P. Lever*. Butterworths, London 1973. 651 pp., bound £4.50. – Plenary lectures at the XIV. International Conference on Coordination Chemistry, 22–28 June 1972 in Toronto/Canada.

Chemistry of Marine Natural Products. By *P. J. Scheuer*. Academic Press, New York–London 1973. XI, 201 pp., bound $ 14.00.

Contents: Isoprenoids; Sterols; Benzenoids; Nitrogenous Compounds; Nonaromatic Compounds with Unbranched Carbon Skeletons.

Advances in Quantum Chemistry, Vol. 7. Edited by *P.-O. Löwdin*. Academic Press, New York—London 1973. XVI, 445 pp., bound $ 29.50.

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The Challenge to Macromolecular Science[**]

By Paul J. Flory[*]

The adaptation of polymeric materials for the artifacts of man originated in antiquity. Techniques for processing fibers, hides, wood, rubber, and naturally-occurring resins have precedents that predate recorded history. These are amongst the oldest technologies that have evolved over the centuries and up to the present. By contrast, the *science* of polymers, or macromolecules, made a late appearance—late, that is, relative to other branches of science. The modern science of molecules that we call chemistry had its beginnings around 1860. The foundations of quantum theory and quantum mechanics were established from 1900 to 1925, the theory of relativity from 1905 to about 1920. The basic concepts underlying macromolecular science were not put forward until after these epoch-making advances had determined the course and content of chemistry and physics for decades to come.

The motif of macromolecular architecture—the concatenation of atoms, or groups of atoms, to form covalently linked chains of great length—did not achieve widespread acceptance as the structural principle pervading virtually all polymeric substances until 1930 and doubts concerning its reality lingered for some years thereafter. Polymeric chemical structures had been suggested—even advocated—as much as 70 years earlier. However, for reasons difficult to grasp in retrospect linear macromolecular structures were rejected in every instance. Instead, small cyclic structures were ascribed to substances now recognized as polymeric, in the molecular sense of this term. Thus, rings of three to twelve members were proposed for proteins, rubber, cellulose, starch, and various synthetically prepared polymers. The preoccupation of chemists in general with molecules representable by concise formulas conveniently expressed on the printed page seems to have generated an overpowering conviction that all substances should be so constituted. The much larger chemical structures suggested from time to time for the most commonplace of substances, and the most important ones in the environment of man, were consistently cast aside, probably on this account.

Not until the late 1920's was it clearly established that cellulose and starch are high polymers consisting at the molecular level of long chains. The epic of natural rubber is similar: determination of the chemical structure of the unit at the beginning of this century, appearance of a variety of cyclic formulas, and finally, in the late 1920's, the belated acceptance of the polymeric chain formula.

The polypeptide hypothesis regarding the chemical structure of proteins put forward by *Hofmeister* and by *Fischer* about 1902 did not gain widespread acceptance before 1930. As late as the mid 1920's leading organic chemists of the period vied with one another in matches of ingenuity to invent esoteric cyclic structures for proteins, all seemingly in a vain effort to avert adoption of the polypeptide chain structure as the pattern for life-giving proteins, the abundance of chemical and physical evidence in support of the polypeptide structure notwithstanding. Evidently the vision of a polymeric structure for materials of such supreme importance was repugnant. Whether the polypeptide chain was regarded as inherently objectionable or merely something to be opposed because it departed from the structures that were in the mainstream of chemists' endeavors is a matter for conjecture. Bear in mind that *Fischer* had completed his *tour de force* in synthesizing a polypeptide of 30 units during the first decade of the century. Yet, even he clung to the belief that proteins consisted of chain molecules no longer than those he had synthesized, a number of these being "colloidally" aggregated to form the protein "particle."

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[**] Based on an address delivered at the dedication of Midland Macromolecular Institute, Midland, Michigan (USA), on September 28, 1972. The text will also appear in the International Journal of Polymeric Materials and in *H.-G. Elias*: Trends in Macromolecular Science (Midland Macromolecular Monographs, Vol. 1), published by Gordon & Breach, New York—London.

The saga of polynucleotides is even more striking. According to opinions that went essentially unchallenged until the mid 1940's, they were tetrameric. Only in the 1950's was it established that they consist of long chains of nucleotide units numbering as many as hundreds of thousands.

Evolution of ideas regarding synthetic polymers followed a similar course. Synthetic polymer chemistry developed rapidly once their molecular nature was understood and hence the skills of the chemist could be turned systematically to their preparation in ever-increasing variety. The influence of the pioneering work of *Staudinger* and *Carothers* in this period cannot be over-estimated. Their work placed the macromolecular hypothesis on a firm footing and at the same time elaborated methods of measurement and synthesis.

It is important to observe that macromolecules are not clearly demarcated from their analogs of lower molecular weight. In every series of macromolecular homologs, species of intermediate chain length occur. The chemical bonds joining atoms in macromolecules are not discernibly different from those in small molecules; they are described by the same geometrical parameters. Any sharply drawn distinction between the domain of the molecules that are commonplace in the laboratory and the macromolecules that are commonplace everywhere else must necessarily be arbitrary. Hence, the science of macromolecules is fundamentally coextensive with the rest of chemistry, and with some of the ramifications of physics too. Not to be overlooked, however, is the inescapable fact that definite alterations in concept and theory are required for the understanding of macromolecules. Knowledge in the domain of giant molecules is not to be gained by simple deduction from concepts and rules gathered for small molecules. Modifications in viewpoint and method are required, and in some respects a different set of guidelines must be adopted.

The relatively late emergence of macromolecular science has had an important consequence that weighs heavily on present and future. The basic pattern of chemistry as a discipline, with its traditional subdivisions, became established prior to the appreciation of the molecular nature of polymers, and prior to the appearance of theories and generalizations describing their behavior. Macromolecules were therefore left out of the syllabus in its formative years. Only a few desultory remarks on colloids found a place in the textbooks, and these were generally misleading, if not wrong altogether. The subject has not gained entry since. Irrespective of one's views on the proper place for polymer chemistry and physics in the curriculum, its virtual absence therein at present is a fact to be reckoned with.

The relevance of polymer science to industrial technology is self-evident, and, I think, widely recognized. I have already alluded to the close temporal correlation between the emergence of polymer science and the proliferation of synthetic polymeric materials. If the former did not in fact furnish the main impetus for the latter, at least it has played a major role in bringing into being what posterity may refer to as the age of polymers. Incidentally, I also believe it is a valid assertion that pure and applied polymer science continue to enjoy a mutually fruitful relationship.

The relevance of polymer science to biology seems not so well appreciated. Custom, and perhaps prejudice rooted in the never-dying vitalistic view of things living, seem to sustain the impression that biopolymers are unrelated to the technological members of the polymer family. To be sure, biopolymers have acquired certain attributes in the course of their evolution that are not shared by their less refined relatives. But there are basic properties and behavioral patterns shared by all polymers: the thermodynamics of their solutions, rules governing their spatial configurations, manifestation of high elasticity under suitable conditions, crystallization, *etc.* The tendency to relegate biopolymers and technological polymers to different categories works to the detriment of the fuller understanding of both. If molecular biology is to rest on a sound *molecular* basis, then logic dictates that that basis be provided by the science of polymeric molecules. For this purpose a polymer science concerned with the fundamentals of macromolecular behavior in the broadest sense is required.

There is a further role for macromolecular science, and one for which it is especially well suited. I refer to the communication between science and the public. Most subjects at the forefront of science pertain to matters abstruse and quite remote from the interests and awareness of the nonspecialist. Chemistry is illustrative: its compounds, theories, and reactions offer relatively few opportunities for cultivation of interest on the part of the public at large. Polymeric materials, being exemplified in profusion in a multitude of articles of commerce, not to mention biopolymers too intimate to require mention, are ideally suited as subjects for communication of science to a wider audience. It is here that polymer science enjoys a special opportunity by virtue of its subject and purview.

Nevertheless, macromolecular science still has a long way to go if it is to meet the challenges I have indicated. Much basic and creative science needs to be carried forward. Coherence of the subject through systematization of existing knowledge is of ever increasing importance as research spreads into new directions. At the same time, the importance of cultivating connections between macromolecular science and related fields should not be overlooked.

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Polymers as Reagents in Organic Synthesis

By C. G. Overberger and K. N. Sannes[*]

Polymeric reagents offer a range of unique advantages. Intramolecular reactions, such as the cyclization of peptides or Dieckmann cyclizations, can be brought about by attaching the reactive molecules at remote points along a polymer chain. In contrast, if the reactive molecules are anchored in close proximity on a polymeric support then intermolecular reactions occur, as demonstrated for a ketone synthesis. Apart from such proximity effects, cooperative effects can also be exploited, *e.g.* in the formation of a 2:1 complex of a crown ether and an alkali metal ion. The hydrolysis of an ester with polyvinylimidazole provides a detailed illustration of hydrophobic interactions. The simple separation of polymer-bound and low-molecular compounds by filtration is another significant advantage.

1. Introduction

One of the first applications of a macromolecule as a "solid support" in organic synthesis has served to revolutionize the field of peptide fabrication. Condensing specific sequences of amino acids onto a growing peptide, which is attached to an insoluble polymer, has, at least in principle, changed peptide synthesis from one of tedious, multi-faceted separations to a procedure which has been automated. No further account[1] of this field will be given in this report except for certain studies which apply to the topic under discussion. Instead, this report contains what we thought to be novel applications of polymeric reagents in synthetic organic chemistry. No attempt at inclusiveness has been made.

2. Proximity Effects

2.1. Dilution or Separation of Reactants

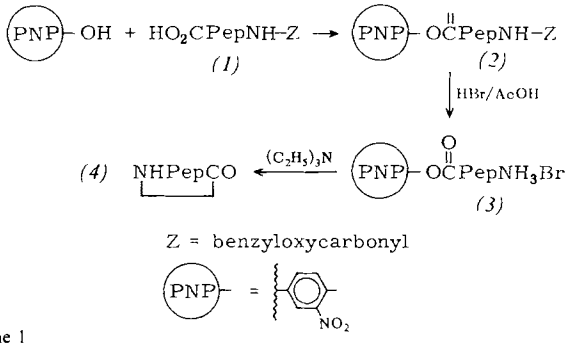
The ability to control the relative rates of competitive reactions in a given system constitutes a good portion of successful synthetic chemistry. In particular, cyclization reactions are successful only when the rate of the intramolecular ring closure reaction is higher than that of the competing intermolecular coupling reaction. Traditionally, high dilution of the reactant has been used to reduce the rates of the latter reaction and thereby increase the amount of desired cyclic product formed. Obviously this method has its limitations.

Another method of limiting the rate of intramolecular reactions consists, in theory, of anchoring each molecule to be cyclized to a functional group along a polymer chain at intervals that preclude intermolecular (strictly speaking "intrapolymeric") reactions.

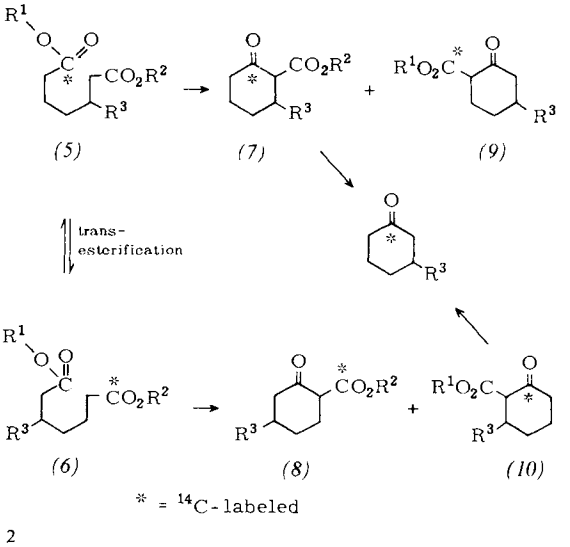
The ring closure of amino acids attached to a polymeric support demonstrates the feasibility of this type of reaction[2, 3].

As outlined in Scheme 1, the *N*-blocked amino acid *(1)* is attached to poly-4-hydroxy-3-nitrostyrene to form the polymer ester *(2)*. Removal of the blocking group affords the amine *(3)* which, upon treatment with triethylamine, undergoes cyclization with simultaneous separation of the newly formed cyclic peptide *(4)* from the insoluble macromolecular support.

Another study has demonstrated the feasibility of performing Dieckmann reactions on diesters which are bonded to solid supports[4]. Potassium salts of ^{14}C-labeled pimelate half esters were treated with either chloromethylated polystyrene or benzyl chloride to form compounds *(5a)*, *(5c)*, *(5e)* and *(5b)* and *(5d)* respectively (Scheme 2). Treatment of *(5a)*, *(5c)*, or *(5e)* with base affords 15—46% yields of cyclized products (Table 1).



Scheme 1



Scheme 2

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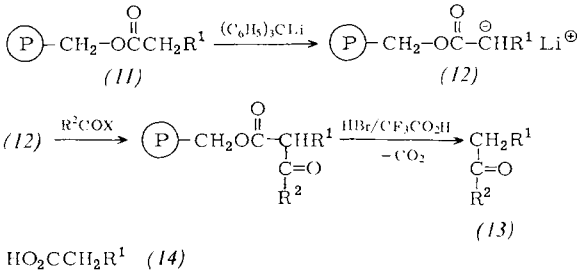
There are additional advantages offered by the solid support system that warrant discussion. For example, *(5b)* affords two cyclic products, the alkyl and benzyl esters *(7b)* and *(9b)* respectively, when treated with base (Table 1). Also, reactions begin to interfere. The successful acylation reactions employed 0.1—0.3 mmol of ester/gram of polymer and competing reactions were evident at concentrations of 1.5—2.0 mmol of ester/gram of polymer.

Table 1. Examples of Dieckmann cyclizations of the diesters *(5)* (see Scheme 2: Ⓟ = polymer).

Cpd.	R^1	R^2	R^3	*(7)* : *(8)*	Yield [mol-%] *(9)* + *(10)*
a	Ⓟ-$C_6H_4CH_2$	$C(C_2H_5)_3$	H	99.69 : 0.31	—
b	$C_6H_5CH_2$	$C(C_2H_5)_3$	H	98.30 : 1.70	10
c	Ⓟ-$C_6H_4CH_2$	$C(C_2H_5)_3$	C_2H_5	97.25 : 2.75	—
d	$C_6H_5CH_2$	$C(C_2H_5)_3$	C_2H_5	96.80 : 3.20	21
e	Ⓟ-$C_6H_4CH_2$	C_2H_5	H	mixture	—

the group R^3 occupies a different relative position on the ring in *(7b)* and *(9b)*. While reaction of *(5a)*, for example, with base might form *(7a)* as well as *(9a)*, the cyclic compound *(9a)* remains attached to the polymer support and can be separated from *(7a)* by filtration. This eliminates the need for the separation of the two similar keto esters as is the case in reactions of *(5b)* and *(5d)*. Evidently a hindered ester [1,1-diethylpropyl in *(5a)* and *(5c)* instead of ethyl as in *(5e)*] must be used to prevent transesterification. Once this has been done, the procedure can serve very nicely in the preparation of specifically labeled ring compounds. As mentioned, this method can probably be extended to systems with various ring sizes.

Successful acylation[5] and alkylation[6] of active methylene esters bound to polymer supports have been reported. Again, in the acylation of active methylene esters the competing self-condensation reaction is reduced to negligible proportions by attaching the active esters at intervals sufficiently large to prevent intrapolymeric reactions. Another undesired reaction, diacylation, is also prevented, presumably for similar reasons. The reactions in Scheme 3 provided a *single* ketone in each case (Table 2). Analogous reactions without the polymer support resulted in several ketonic compounds. Reasonably, it was observed[5] that if the concentration of ester bound to the polymer becomes too high the intrapolymeric

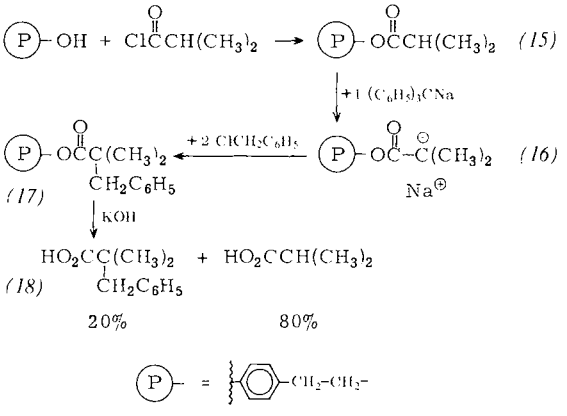


Scheme 3

Table 2. Examples of the preparation of ketones *(13)* with polymer-supported esters *(11)* having active methylene groups (see Scheme 3; Ⓟ = polystyrene).

R^1	R^2COX	*(13)*, yield [%]	*(14)*, recovered [%]
C_6H_5	*p*-$NO_2C_6H_4COCl$	43	40
C_6H_5	*p*-BrC_6H_4COCl	40	45
C_6H_5	$(\alpha\text{-}C_{10}H_7CH_2CO)_2O$	40	55
H	*p*-$NO_2C_6H_4COCl$	20	45

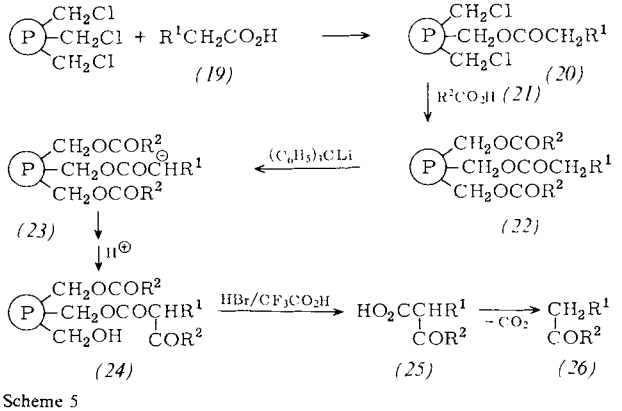
The alkylation of isobutyric acid[6] which was esterified onto a non-benzylic support, as depicted in Scheme 4, afforded only 2,2-dimethyl-3-phenylpropionic acid *(18)* and unreacted isobutyric acid in 20 and 80% yields, respectively.



Scheme 4

2.2. Forced Combination of Moieties Connected to the Same Macromolecule

In contrast to the effect obtained by separating interreactive molecules by bonding them remotely on a macromolecule, a system could, in principle, be constructed with two types of molecules held in close proximity in order to promote this "intrapolymeric" reaction. In practice this type of proximity effect is involved in the reaction outlined in Scheme 5[7].



Scheme 5

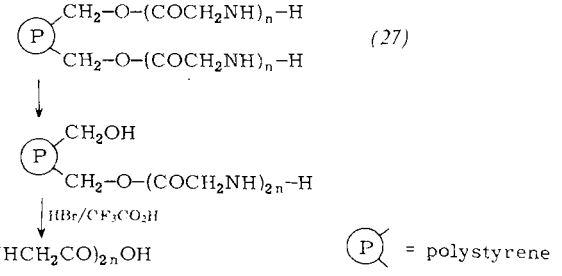
A small percentage (2.3—2.5%) of chloromethylated polystyrene groups were esterified with a limited amount of an enolizable acid *(19)* and the remainder of the groups with a nonenolizable acid *(21)* to give the mixed ester *(22)*. The addition of base results in internal condensation to form *(24)* which after esterolysis and decarboxylation provides *only* ketone *(26)* and starting acids *(19)* and *(21)* (Table 3). Analogous

Table 3. Examples of intrapolymeric synthesis of ketones *(26)* with enolizable acids $R^1CH_2CO_2H$ *(19)* and nonenolizable acids R^2CO_2H *(21)* (see Scheme 5, Ⓟ = polystyrene).

R^1	R^2	*(26)*, yield [%]	Yield [%] in analogous reaction in solution
$CH_3(CH_2)_5$	*p*-ClC_6H_4	35	30
C_6H_5	C_6H_5	45	—
$C_6H_5CH_2$	C_6H_5	85	42
$CH_3(CH_2)_3$	C_6H_5	95	—
$C_6H_5CH_2$	*p*-ClC_6H_4	85	20

reactions under similar conditions but without the polymer support lead to a more complex mixture of products. The intrapolymeric nature of the reaction *(23)*→*(24)* in Scheme 5 is evidenced by the fact that no ketone was observed when two batches of polymeric esters—one with an enolizable and one with a nonenolizable ester—were reacted and worked-up under conditions similar to those used for *(22)*. This finding is in line with the fact that a larger ratio of $R^2:R^1$ in *(22)* results in higher yields of *(26)*.

In the solid-phase synthesis of peptides, side-reactions limit the length of the peptide chain that can be obtained in purified form. Thus a "chain doubling" reaction (Scheme 6) resembling



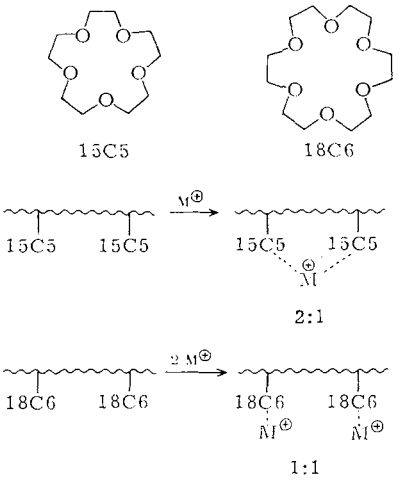
Scheme 6

the condensation of two esters bound to a polymer chain has been reported in the Merrifield synthesis of peptides[8]. Chain doubling takes place only when the distance between peptide residues on *(27)* permits its occurrence. The study in question used 0.5 to 0.7 mmol of peptide/gram of peptide resin. A lower concentration of peptide residues would tend to reduce chain doubling. Other factors that may prove to be important in these intrapolymeric reactions are the chain length of peptide, the nature of the polymeric leaving group, degree of cross-linking of the support, and the solvent system.

3. Cooperative Effects

The fact that juxtaposition of reactive moieties can be "ensured" if they are pendant groups of a polymer is the basis of another advantage of polymeric reagents which has been termed "cooperative effects". In a polymer the reaction of two pendant groups with a third molecule from the solution mimics a bimolecular reaction which has much less stringent entropy requirements than a termolecular reaction in solution. This phenomenon has been called on to explain kinetic results of enzyme prototype systems.

Recently, complexes of alkali metal ions with either polymeric crown ethers or their monomeric crown ether analogs have been studied[9]. The cyclic monomeric ethers 15C5 and 18C6 (Scheme 7) form 2:1 and 1:1 complexes, respectively, with



Scheme 7

fluorenylpotassium in THF, and solid complexes with KCNS. Available evidence points toward the same stoichiometry with polymeric ethers. This difference in the stoichiometry of 15C5 and 18C6 ethers has been reasonably attributed to the difference in ring diameter of the two ethers. The generally larger ratios of polymeric to monomeric complexing strength in the 15C5 ether systems compared to the corresponding ratios in the 18C6 system (Table 4) can be readily explained by assuming that two crown units complex with each alkali metal ion in the former system. Two crown units are held in close proximity in the polymer, and the "polymeric" 2:1 complex would form more readily than would the three-unit complex in the 15C5 monomeric system. The difference between polymeric and monomeric systems would not be expected to be so great for the 1:1 complexes.

Table 4. Ratios of complexing abilities of analogous polymeric *versus* monomeric crown ethers (Ⓟ = polymer, 15C5 and 18C6, see Scheme 7).

M^+	Ⓟ-15C5 : 15C5	Ⓟ-18C6 : 18C6
Li^+	>10 : 1	6.2 : 1
Na^+	2.3 : 1	1.6 : 1
K^+	3.8 : 1	1.1 : 1
Rb^+	6.4 : 1	1.1 : 1
Cs^+	19.7 : 1	

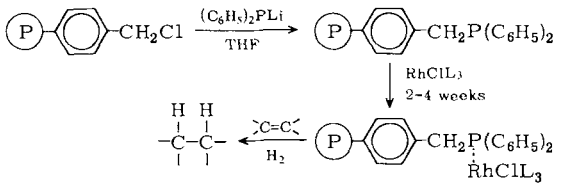
4. Selectivity of Substrate

4.1. Influence of Size

If the active site of a macromolecule is located inside a semiordered insoluble polymer, it is not difficult to visualize a situation in which the rate of reaction of substrates would depend

on their ability to gain access to this active site. For example, the size of a molecule would certainly be one such factor.

A system such as is described above has been reported in a study in which the selective hydrogenation of olefins was demonstrated with a polymer-supported rhodium(I) catalyst *(28)* (Scheme 8)[10]. As Table 5 shows, the relative rate of



Scheme 8 *(28)*

hydrogenation of cyclic olefins depends upon the size of the ring when the catalyst is coupled to a macromolecule as in *(28)*, while this effect is not evident with tris(triphenylphosphane)rhodium(I) chloride as catalyst.

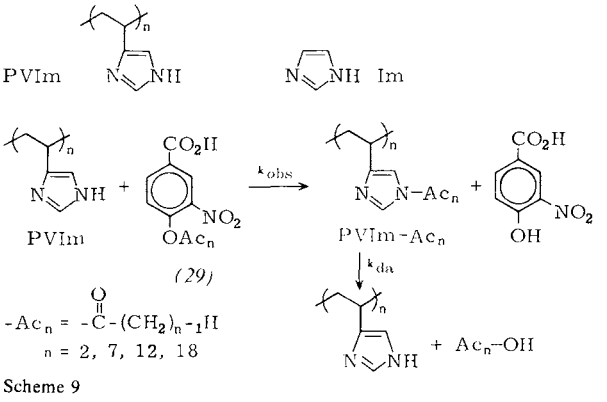
Table 5. Examples of hydrogenation rates of cyclic olefins with polymer-bound catalyst *(28)* and with $RhCl[P(C_6H_5)_3]_3$ (2.5 mmol/l) (see Scheme 8; Ⓟ = polymer).

olefin	Relative rate	
	(28)	$RhClL_3$
cyclohexene	1	1
cyclooctene	0.39	1
cyclododecene	0.22	0.67
2-cholestene	0.03	0.72

4.2. Hydrophobic Effects and Interactions

In aqueous solutions, apolar (hydrophobic) bonding between two hydrophobic molecules has been shown to increase the rate of hydrolysis of esters by polymeric catalysts.

Hydrolysis of the ester bond in 3-nitro-4-dodecanoyloxybenzoic acid *(29)*, n = 12 (Scheme 9) with the synthetic, macromo-



Scheme 9

lecular catalyst polyvinylimidazole (PVIm)[13] was *ca.* 10^3 times as fast as with monomeric imidazole (Im)[14]. These hydrolysis rates were found to be critically dependent on the chain length of the acyloxy group of the substrate and on the solvent composition. The bulk of the rate enhancement was thus attributed to apolar (hydrophobic) association of catalyst and substrate.

During the study of the polyvinylimidazole- and imidazole-catalyzed hydrolyses of the ester *(29)* in ethanol-water mixtures of various compositions a very interesting autocatalytic or *accelerative kinetic pattern* was observed (see Fig. 1). The rate of the reaction continuously increased so that at 75% completion the rate was *ca.* 5 times faster than the initial rate.

On observing the deacylation rates of the polymeric acyl imidazoles PVIm—Ac_n (see Scheme 9), it was noted that for the cases exhibiting the accelerative behavior, deacylation of the intermediate was the rate-determining step. This again demonstrates the influence of apolar bonding on the rates of ester hydrolysis. The acylated polymer is more hydrophobic than the non-acylated polymer.

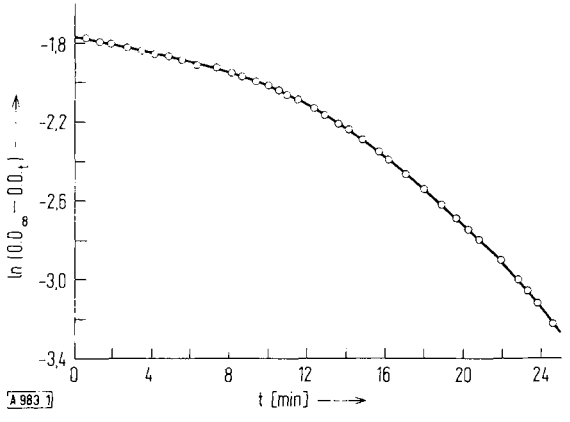


Fig. 1. Kinetics of the accelerative pseudo-first-order hydrolysis of the ester *(29)*, $n = 12$, 40 vol% C_2H_5OH/H_2O, $[PVIm] = 5.0 \times 10^{-4}$ mol/l [*(29)*, $n = 12$] $= 5.0 \times 10^{-5}$ mol/l, $\mu = 0.02$, [Tris buffer] = 0.02 mol/l, pH = 8.0, 26 °C. O.D. = optical density.

Table 6 shows the surprisingly large dependence of the deacylation rate on the chain length of the acyl group. This observation

Table 6. First-order rate constants for hydrolysis of esters *(29)* and deacylation of the intermediate (see Scheme 9 and Figure 1) [a].

(29), *n*	k_{obs} [min^{-1}] [b]	k_{da} [min^{-1}] [c]
2	0.022	0.250
7	0.013	0.242
12	0.090 [d]	0.041
18	0.500 [d]	0.006

[a] 40 vol% ethanol/water, $\mu = 0.02$, pH = 8.0, 26 °C.
[b] [PVIm] $= 5.0 \times 10^{-4}$ mol/l, [*(29)*] $= 5.0 \times 10^{-5}$ mol/l.
[c] Determined for > 90% deacylation completed; deacylation is accelerative.
[d] Accelerative kinetic behavior, k_{obs} at *ca.* 75% reaction.

is rationalized by considering formation of a polysoap-like structure as the polymer is increasingly acylated with long-chain groups[15].

Figure 2 shows the effect of varying the degree of acylation of PVIm with dodecanoic acid on the hydrolyses of *(29)*, $n = 7$, and *(29)*, $n = 2$. Particularly for *(29)*, $n = 7$, the rate increased as the content of long-chain acyl groups increased. These results served to elucidate the cause of the accelerative behavior[15]. Progressive intramolecular micellarization occurring along the polymer chain creates an increasingly nonpolar molecule. This results in an enhancement of the apolar associa-

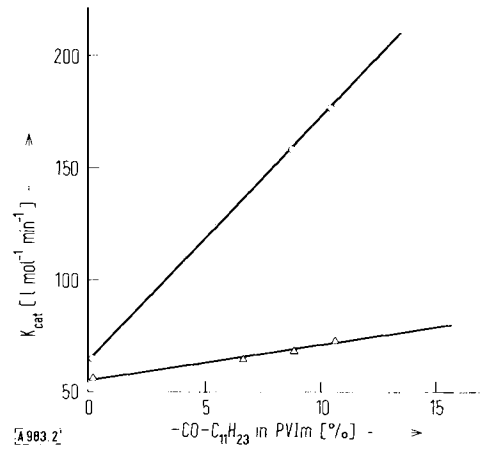


Fig. 2. Catalytic hydrolysis of the esters *(29)*, $n=7$ (O—O) and *(29)*, $n=2$ (Δ···Δ) with PVIm having various degrees of dodecanoylation. 33 vol% C_2H_5OH/H_2O, $\mu=0.02$, [Tris buffer] = 0.02 mol/l, pH = 8.0, 26 °C.

tion of substrate and catalyst. Undoubtedly, a conformational change accompanies this process of polysoap formation which is evidenced through the kinetics of the hydrolysis reaction.

The situation described above may be considered conceptually similar to the *allosteric effect* displayed by certain enzyme systems[16]. The catalytic function of enzymes may be affected and controlled by interaction with small molecules, not only directly, at the active site, but also indirectly, at distant, secondary allosteric sites. Generally, a conformational change accompanies the appearance of allosteric phenomena. The accelerative behavior is evidence of a conceptually similar occurrence in the case of the synthetic, macromolecular catalyst, polyvinylimidazole.

Hydroxylamine is known to be more than 10^5 times as effective as water in acyl transfer from acetylimidazole[17]. Figure 3 demonstrates the effect of added hydroxylamine on the

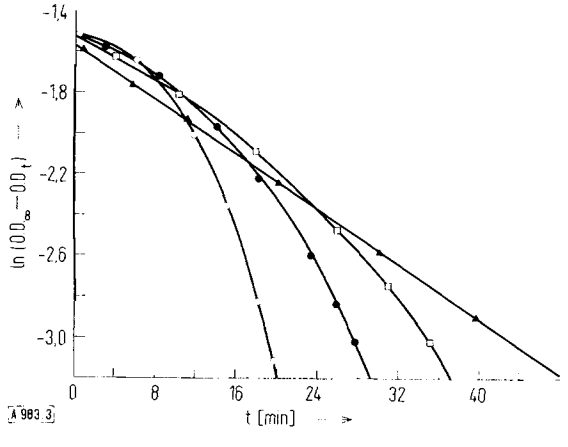


Fig. 3. Effect of increasing concentration of hydroxylamine on accelerative behavior in the hydrolysis of the ester *(29)*, $n=12$. 40 vol% C_2H_5OH/H_2O, [PVIm] = 5.0×10^{-4} mol/l, [*(29)*, $n=12$] = 5.0×10^{-5} mol/l (O—O); with [NH_2OH] = 3.0×10^{-4} mol/l (●—●); 4.5×10^{-4} mol/l (□—□); 11.1×10^{-4} mol/l (▲···▲). O.D. = optical density.

accelerative behavior. The acceleration diminishes with increasing hydroxylamine content in the system; this can be explained by a decrease in the concentration of the intermediate. Eventually, the accelerative behavior is completely eliminated, indicating that the intermediate is being destroyed at a faster rate than the substrate is being hydrolyzed.

The viscosity of PVIm in ethanol/water mixtures of various compositions (Fig. 4) indicates a contraction of the macromole-

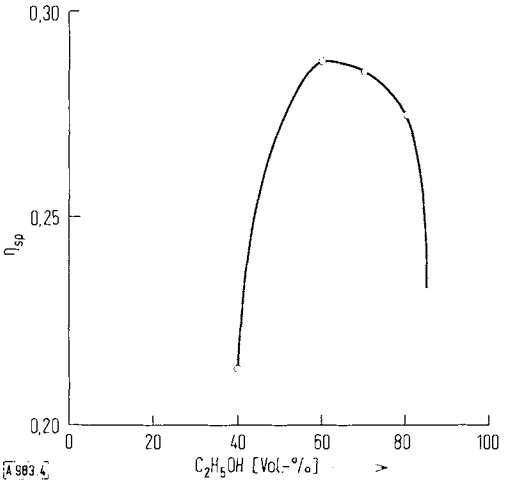


Fig. 4. Solution viscosity of polyvinylimidazole as a function of ethanol concentration (ethanol-water); [PVIm] = 4.229 (g/l), $\mu=0.02$, 26 °C.

cule in low and high ethanol compositions[18]. Shrinkage of the polymer coils at low ethanol contents might be the result of intra- and inter-molecular nonpolar interactions, whereas

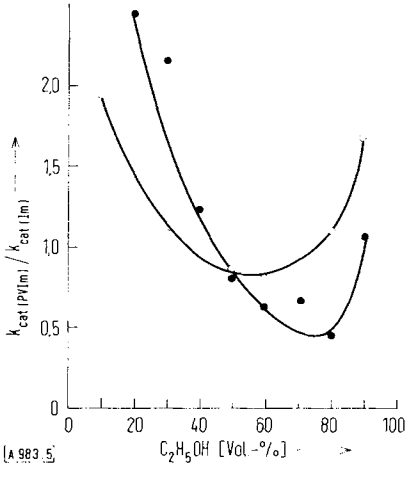


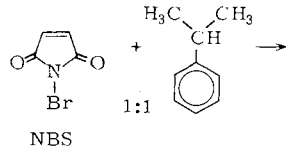
Fig. 5. Ratios of the rate constants for polyvinylimidazole- and imidazole-catalyzed solvolysis of *p*-nitrophenyl acetate (O—O) and of *p*-nitrophenyl heptanoate (●—●) as function of the ethanol concentration (ethanol-water). pH ≈ 8, $\mu=0.02$, 26 °C.

that in solvents of high ethanol content is ascribed primarily to intra- and inter-molecular hydrogen bonding[18]. Figure 5 shows the kinetic manifestation of this conformational process for the hydrolysis of *p*-nitrophenyl acetate and *p*-nitrophenyl heptanoate.

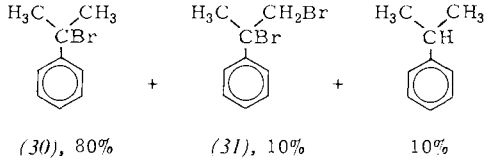
5. Change in Mechanism

The bromination of cumene with *N*-bromosuccinimide (NBS) in carbon tetrachloride results in the expected benzylic bromination product *(30)* and a dibromo product *(31)* (Scheme 10). However, when poly-*N*-bromosuccinimide (poly-NBS), prepared by bromination of polymaleimide, was used as the brominating agent (1.5 h in CCl_4 with benzoyl peroxide), a

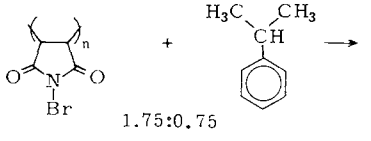
completely different set of products was obtained (Schemes 10 and 11)[11]. (The bromine comes from reaction of poly-NBS



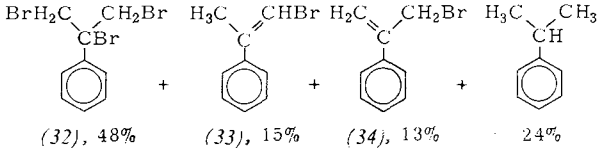
NBS



(30), 80% *(31)*, 10% 10%



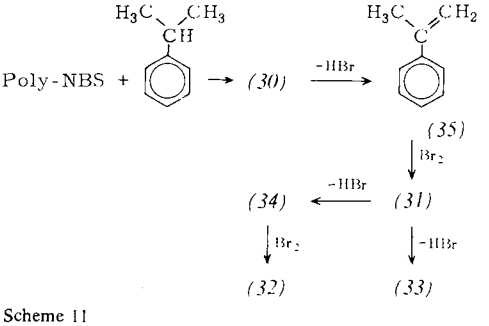
Poly-NBS



(32), 48% *(33)*, 15% *(34)*, 13% 24%

Scheme 10

and HBr.) This demonstrates another feature of macromolecular reagents; that of a change in mechanism upon anchoring the functional moiety to a large carrier molecule.

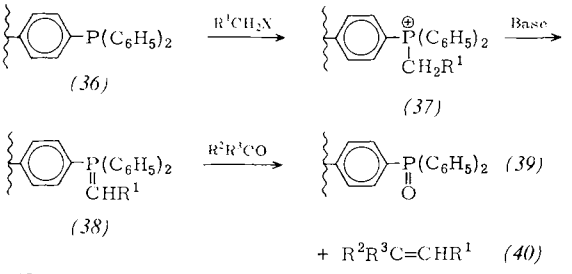


Scheme 11

The polar medium provided by neighboring succinimide units in poly-NBS may be responsible for the changed mechanism (especially the repeated dehydrobromination) and different products obtained. This idea is substantiated by the fact that the bromination of cumene with NBS in a *more polar* solvent, acetonitrile, results in products similar to those obtained with poly-NBS in carbon tetrachloride.

6. Simple Separation of Polymeric Reagent

Polymeric phosphoranes *(38)* have been prepared (Scheme 12) and reacted with carbonyl compounds to form olefins[12].



Scheme 12

These Wittig reactions on polymeric supports afford product yields comparable with monomeric reactions but the removal of the phosphane oxide formed in the reaction is accomplished by simply filtering off the polymer to which the P—O unit *(39)* remains attached. As in solid phase peptide synthesis, the main advantage lies in the ease of separation.

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[1] For a good account see *G. R. Stark:* Biochemical Aspects of Reactions on Solid Supports. Academic Press, New York 1971, Chapter 3.

[2] *M. Fridkin, A. Patchornik*, and *E. Katchalski*, J. Amer. Chem. Soc. *87*, 4646 (1965).

[3] *A. Patchornik, M. Fridkin*, and *E. Katchalski*, Proc. Eur. Peptide Symp. 8th, Noordwijk *1967*, 91.

[4] *J. I. Crowley* and *H. Rapoport*, J. Amer. Chem. Soc. *92*, 6363 (1970).

[5] *A. Patchornik* and *M. A. Kraus*, J. Amer. Chem. Soc. *92*, 7587 (1970).

[6] a) *F. Camps, J. Castells, M. J. Ferrando*, and *J. Font*, Tetrahedron Lett. *1971*, 1713; b) *M. A. Kraus* and *A. Patchornik*, Isr. J. Chem. *9*, 269 (1971).

[7] *M. A. Kraus* and *A. Patchornik*, J. Amer. Chem. Soc. *93*, 7325 (1971).

[8] *H. C. Beyerman, E. W. B. De Leer*, and *W. van Vossen*, J. C. S. Chem. Comm. *1972*, 929.

[9] *S. Kopolow, T. E. Hogen*, and *J. Smid*, Macromolecules *4*, 359 (1971); cf. *C. J. Pedersen* and *H. K. Frensdorff*, Angew. Chem. *84*, 16 (1972); Angew. Chem. internat. Edit. *11*, 16 (1972).

[10] *R. H. Grubbs* and *L. C. Kroll*, J. Amer. Chem. Soc. *93*, 3062 (1971).

[11] *C. Yaroslavsky, A. Patchornik*, and *E. Katchalski*, Tetrahedron Lett. *1970*, 3629.

[12] a) *S. V. McKinley* and *J. W. Rakshys*, J. C. S. Chem. Comm. *1972*, 134; b) *F. Camps, J. Castells, J. Font*, and *F. Vela*, Tetrahedron Lett. *1971*, 1715.

[13] For a review see *C. G. Overberger* and *J. C. Salamone*, Macromolecules *2*, 553 (1969).

[14] *C. G. Overberger, M. Morimoto, I. Cho*, and *J. C. Salamone*, Macromolecules *2*, 553 (1969).

[15] *C. G. Overberger* and *R. C. Glowaky*, J. Amer. Chem. Soc., in press.

[16] *H. R. Mahler* and *E. H. Cordes:* Biological Chemistry. 2nd Edit. Harper and Row, New York 1971, p. 299.

[17] *W. P. Jencks* and *J. Carrioulo*, J. Biol. Chem. *234*, 1272, 1280 (1959).

[18] *C. G. Overberger* and *M. Morimoto*, J. Amer. Chem. Soc. *93*, 3222 (1971).

Mechanical Fabrication of Thermoplastic Polymers[**]

By Turner Alfrey[*]

One of the most important features influencing the mechanical behavior of a fabricated thermoplastic item is the spatial arrangement of the polymer molecules. *Inter alia* processes developed for controlling the pattern of orientation of the polymer molecules are discussed.

1. Introduction

The mechanical fabrication of thermoplastic polymers embraces a wide range of operations. Some processes, such as extrusion and injection molding, are carried out at high temperatures where the polymers behave as viscoelastic fluids. Other processes, such as bottle blowing and vacuum forming, entail only moderate deformations, and can be carried out at temperatures where the polymers behave as viscoelastic solids. Some thermoplastic polymers are capable of being fabricated at still lower temperatures (below the glass temperature for amorphous polymers; below the melting point for crystalline polymers), by processes similar to the rolling, forging, and drawing of metals. In some processes, a crystallizable polymer enters the fabrication zone in a metastable, supercooled amorphous state, and crystallization occurs during the mechanical deformation.

The primary purpose of any fabrication operation is, of course, the establishment of a desired geometrical shape. A less apparent, but most important, feature which is simultaneously established is the spatial arrangement of the polymer molecules within the fabricated article. This includes orientation in amorphous polymers, morphology and orientation in crystalline polymers, and phase geometry in multiphase systems such as composites and foams.

The physical properties and performance of fabricated thermoplastic items depend upon the molecular structure (mainly established during polymerization) and the spatial arrangement of the polymer molecules (established during fabrication).

2. Amorphous Thermoplastics

Consider first the influence of molecular orientation in amorphous thermoplastics, using atactic polystyrene as a specific example. At room temperature, unoriented polystyrene is a brittle, glassy, amorphous polymer. Uniaxially oriented polystyrene is highly *anisotropic*. In the direction of orientation it can have a high tensile strength and ductile extensibility, and resistance to environmental stress-crazing and cracking[1]. On the other hand, in the transverse direction it is even weaker and more susceptible to stress-cracking than unoriented polystyrene[2]. The tensile strength in the orientation direction increases monotonically with increasing level of orientation, while the elongation-to-break rises to a maximum and then decreases.

Molecular orientation occurs inevitably in most mechanical fabrication operations, the pattern of orientation in the part being governed by the process *kinematics*—the pattern of flow and deformation followed by the polymer during fabrication. The *effects* of orientation can be either favorable or unfavorable, depending on the directions of orientation relative to the stresses encountered in service. Planned, controlled molecular orientation can be a valuable aid in achieving optimum properties and performance. Uncontrolled orientation will have beneficial effects only by accident; usually it is a source of weakness and failure. Controlled molecular orientation in fabricated polymeric articles can be classified as uniaxial, biaxial, or "crossed".

Fibers and monofilaments are subjected in service mainly to tensile and bending loads; and consequently, uniaxial orientation can provide satisfactory mechanical performance. Natural fibers, such as cotton and silk, exhibit molecular orientation, and most synthetic fibers are subjected to controlled uniaxial orientation during manufacture.

Apart from fibers and monofilaments, most thermoplastic articles are subjected to multiaxial stresses in service. In films, sheets, and thin-walled vessels, biaxial stresses are usual. Consequently, uniaxial orientation is often detrimental in such items, whereas biaxial orientation can often be employed to advantage. Biaxially oriented polystyrene sheets (*e.g.* stretched 3:1 in both directions at 110 °C) are strong and tough in all directions in the plane. Tensile strength, impact strength, and resistance to stress-cracking agents are all strongly enhanced, compared with unoriented polystyrene[3]. Biaxially oriented high impact polystyrene exhibits improved strength, impact strength, and fatigue resistance.

"Crossed" molecular orientation was employed by *Cleereman*, who rotated the core of the mold during injection molding of thin-walled polystyrene tumblers[4]. The direction of molecular orientation varied through the wall, in a fashion similar to cross-laminated plywood. This led to a threefold increase in hoop strength, and a 10000-fold increase in time-to-fail in a stress-cracking test in which tumblers were filled with corn oil or motor oil and pressurized. Such tumblers with crossed molecular orientation can be used as parisons for a subsequent bottle-blowing operation, yielding blown bottles with superior properties.

3. Crystalline Thermoplastics

Molecular orientation is also important in crystalline polymers, although the pattern of behavior does not exactly

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parallel that exhibited by glassy amorphous polymers. For example, *Kresser*[5] has reported that the tensile strength of polypropylene systematically increases (approximately four-fold) with increasing uniaxial orientation, while the elongation-to-break systematically decreases. In any particular application, the optimum level of orientation represents a compromise in which both strength and toughness must be given consideration. Furthermore, in crystalline polymers, orientation can be introduced in two fundamentally different fashions:

1. A crystallized specimen can be stretched at a temperature which is higher than the glass transition point but lower than the melting point of the crystal. This requires extensive reorganization of the original crystal morphology.

2. Molten polymer can be oriented, followed by crystallization of the oriented melt. The crystal morphology so obtained, and the resulting physical properties, are different from those obtained by stretching already crystalline polymers.

Clark and *Garber*[6] have emphasized the effects of mechanical processing on the morphology and properties of crystalline polymers, in the cases of blown film, injection-molded specimens, and spun fibers. For example, blown polyoxymethylene film exhibits row-nucleated ("shish-kebab") morphology, and much higher elongation than *spherulitic* polyoxymethylene. Injection molding of polyoxymethylene yields a skin-core structure: a skin layer formed from multiple nuclei under high shear stress during filling; a continued growth inward of twisting lamellae after mold filling; and a spherulitic core nucleated and crystallized under quiescent conditions.

4. Films

The manufacture of Saran film involves a biaxial orientation step carried out in a bubble, at a temperature below the melting point of the crystal. Molten (but crystallizable) polymer is extruded as a tube, and rapidly quenched past the crystallization range. This metastable, supercooled, amorphous tube is passed between nip-rolls into a bubble zone of trapped air. Here the tube undergoes both machine-direction and circumferential stretching, which induces crystallization. The product, a biaxially oriented, crystalline, thin-walled tube, is passed through converging rolls and nip-rolls, and either slit or wound up as a flattened tube. Machine direction orientation can be made greater, equal, or less than the circumferential orientation by controlling mechanical variables in the bubble zone. Mechanical properties in the two directions, and shrinkage characteristics, can be made balanced or unbalanced, as called for in various specific end uses[7].

Such bubble processes belong to a class of operations which are susceptible to complete mechanical analysis—namely those involving membranes of rotational symmetry[16]. This class includes both batch operations such as vacuum forming and continuous operations. In all these operations, whether batch or continuous, certain common features are encountered—namely, the geometry of rotationally symmetric surfaces, and the equations of equilibrium for membranes of rotational symmetry. The meridianal direction and the "hoop" direction, by symmetry, are also principal directions of stress and strain (as well as of curvature). The third principal direction is normal to the surface; and the stress in this direction can be taken as zero. The stress at any point is thus specified by two components: σ_M and σ_H[*]. These principal stresses are everywhere non-negative in the processes under consideration. Since we usually are dealing with large deformations of a nearly incompressible material, it is usually convenient to define the state of deformation in terms of the two principal extension-ratios, λ_M and λ_H. If the material properties are simple, a complete predictive mechanical analysis can be made, by combining the laws of geometry, the equations of equilibrium and the material properties. In the Saran film process, where crystallization accompanies deformation, such a predictive analysis is impossible. Even so, a complete mechanical analysis can be made by setting the process into steady state operation, and then making the following measurements: (a) the air pressure in the bubble; (b) the machine tension; (c) the meridianal curve, $r(z)$; (d) the location of a moving particle along the meridian, as a function of time.

With this information, the equations of equilibrium can be used to calculate $\sigma_M(z)$ and $\sigma_H(z)$. The extension ratios, λ_M and λ_H, can be calculated for every point in the stretching zones. The trajectories on the biaxial stress plane and the biaxial extension-ratio plane can now be plotted, with the aim of correlating them with the directional physical properties of the product.

Some thermoplastic polymers can be fabricated at relatively low temperatures, by methods similar to those used in metal fabrication (crystalline polymers below their melting points; amorphous polymers below their glass temperatures). These low-temperature operations, such as cold rolling[8], drawing[9], and forging[10], invariably introduce large orientations which strongly influence the mechanical performance of fabricated parts. In low temperature forming, the polymer must yield in a ductile manner, rather than fracture. This eliminates many thermoplastic materials; but sometimes mechanical pretreatment can convert an unusable thermoplastic to a usable condition. For example, polystyrene is too brittle to cold-roll, but *oriented* polystyrene can be cold-rolled and further oriented[8].

5. Multiphase Systems

In multi-phase systems, such as composites and foams, another aspect of spatial arrangement is encountered. This is the geometrical disposition of the phases, which is established during fabrication.

The use of fibrous composites to achieve outstanding mechanical performance goes back to ancient times, and in recent years the role of fiber geometry has been the subject of intensive study[12]. In cross-plied laminates, the properties of a ply depend upon the mechanical properties of fiber and matrix material, and the geometrical arrangement within the ply; properties of the laminate depend upon the anisotropic properties of the individual plies and the geometry of their arrangement in the composite. The geometrical disposition of fibers in flexible composites, such as automobile tires, is as decisive a factor as in rigid structural composites.

Phase geometry is also important in laminar composites. Some sword-makers of early times hammered down alternate layers of hard and soft steel, obtaining blades which would take a fine cutting edge and yet were strong and tough[13]. Today,

[*] Subscript M: meridianal direction; subscript H: hoop direction.

many multilayer thermoplastic film laminates are manufactured which exhibit combinations of properties which cannot be matched by any one of the constituent thermoplastic materials. For example, films containing alternating "hard" and "soft" layers can exhibit mutual interlayer mechanical reinforcement. Thin layers of a high modulus, low elongation material, sandwiched between thin adhering layers of a high elongation material, may be prevented from undergoing transverse fracture; and thereby forced to undergo large ductile deformations when the composite is stressed[14]. Such a layered composite has both a high modulus and a high elongation-to-break; it has a much higher work-to-break than any of the individual layers. It is possible to prepare multilayer plastic films containing up to hundreds of parallel layers, by co-extrusion from the melt. The geometrical arrangement of the phases in such a multilayer film is controlled by the flow-pattern developed during the mechanical fabrication operation. One method of developing such flow patterns has been described by *Schrenk et al.*[11]. Different molten polymers are introduced as radial layers into an annular channel and pumped down the channel while the inner shaft, the outer cylindrical surface, or both are rotated. The molten polymer follows helical flowlines of varying pitch, and the initially thick radial layers are twisted into thin spiral laminae. The eventual layer distribution in the tubular film depends in a predictable manner upon the feed-port geometry, the volumetric rates of the various polymers, and the angular velocities of the two rotatable surfaces.

Finally, polymeric *foams* represent a broad class of multiphase systems whose properties depend upon phase geometry as well as upon the material properties of the bulk polymers. Expanded polymers range from elastomeric through semi-rigid (*e.g.*, polyethylene) to rigid[15]. They can be high-density or low-density; open-celled or closed-celled; linear or cross-linked; amorphous or crystalline. They can be directly utilized as end-products, or incorporated into structures such as sandwich panels, which efficiently utilize their unique density-property characteristics.

Over the years, much progress has been made in the understanding of molecular structure of polymers, and in the controlled synthesis of desired molecular structures. Molecular weight distributions, degree of stereoregularity, copolymer sequence distributions, and related molecular features are most important in determining mechanical properties. But in many cases the supramolecular structure, subsequently established by mechanical means, is equally important in determining the performance of a fabricated item.

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[1] *K. J. Cleereman, H. J. Karam*, and *J. L. Williams*, Mod. Plast. *30*, No. 5, p. 119 (1953).

[2] *L. J. Broutman* and *F. J. McGarry*, J. Appl. Polym. Sci. *9*, 609 (1965).

[3] *L. S. Thomas* and *K. J. Cleereman*, SPE (Soc. Plast. Eng.) J. *28*, No. 4, p. 6, No. 6, p. 9 (1972).

[4] *K. J. Cleereman*, SPE (Soc. Plast. Eng.) J. *23*, No. 10, p. 43 (1967); *25*, No. 1, p. 56 (1969).

[5] *T. O. Kresser:* Polypropylene. Reinhold, New York 1960.

[6] *E. S. Clark* and *C. A. Garber*, AIChE Materials Eng. and Sci. Div., Biennial Conference 1970.

[7] *W. R. R. Park:* Plastics Film Technology. Reinhold, New York 1969.

[8] *L. J. Broutman* and *R. S. Patil*, Polym. Eng. Sci. *11*, 165 (1971).

[9] *H. L. Li, P. J. Koch, D. C. Prevorsek*, and *H. J. Oswald*, J. Macromol. Sci. (Phys.) *B4*, 687 (1970).

[10] *K. F. Wissbrun*, Polym. Eng. Sci. *11*, 28 (1971).

[11] *W. J. Schrenk* and *T. Alfrey, Jr.*, ACS Symposium on Coextruded Plastics Films, Fibers, and Composites, Boston, April 1972.

[12] *J. E. Ashton* and *J. C. Halpin:* Primer on Composite Materials. Technomic Publishing Company, Stamford 1969.

[13] *G. Slayter*, Sci. Amer. *206*, No. 1, p. 124 (1962).

[14] *W. J. Schrenk* and *T. Alfrey, Jr.*, Polym. Eng. Sci. *9*, 393 (1969).

[15] *R. E. Skochdopole*, Encycl. Polym. Sci. Technol. *3*, 80 (1965).

[16] *T. Alfrey*, Appl. Polym. Symp. *17*, 3 (1971).

Polymers in Medicine[**]

By Donald J. Lyman[*]

The problems encountered in the use of artificial materials in the body are discussed, using as example the artificial heart. In the quest for suitable materials, numerous investigations have been carried out, including, *inter alia*, studies on the adsorption of proteins on polymer surfaces and on the passivation of such surfaces by coating with proteins or by the growth of cell cultures. The development of passive artificial substances is also discussed.

1. Introduction

The use of materials in the body to repair or restore damaged, diseased, or ravaged tissue and organs is not new. The first recorded use was that of a gold plate in 1588 to repair a cleft palate. Later in the 1800's, there were numerous reports on the use of metal plates and pins to fix broken bones. However, with the advent of the polymer industry and the ready availability of a variety of materials (polymers) having properties more similar to the body, there was a tremendous increase—particularly since the middle 1950's—in the use of materials in surgery.

These uses have been quite broad, ranging from temporary assist materials, such as sutures, staples, surgical adhesives, plasma extenders, bone pins and braces, to relatively simple artificial parts of a more permanent nature, such as vascular grafts, heart valves, hydrocephalic drain tubes, joints, reinforcing meshes, as well as a variety of soft tissue replacement materials for cosmetic surgery, to the more complex devices such as the artificial kidney, the artificial lung, and the artificial heart, which can duplicate some physiological process.

Indeed the imagination and skill of the surgeon and the support and technical assistance from industrial companies have resulted in a great variety of devices being available (see Table 1). However, even with all these successes there have been many failures, most of which have been due to improper choice of material for the intended use. These materials are not inert in the body, but react on and are in turn acted on by the biological environment[1]. Moreover, the materials often tried were those readily available from many commercial processes and did not have the purity and reproducibility that we would like in a biomedical material.

Table 1. Present and possible uses of biomaterials (polymers) in the body.

Arteries, bladder, bladder stimulator, blood, blood-pressure regulator, bone, bone plate, breast, chin, cornea, diaphragm, disc, ear cartilage, elbow, elbow joint, eyeball, fallopian tube, finger joint, heart, heart valve, Herrington rod, hip joint, hydrocephalus shunt, inner ear, intrauterine device, jawbone, kidney, knee joint, liver, lunate, lung, nerve scaffolding, nose cartilage, radial head, reinforcing mesh, shoulder joint, skin, skull, tendon, testicle, toe, trachea, trapezium, ulnar head, ureter.

Medical advances in this field have been highly dependent on the availability of new polymers, which would not only satisfy a variety of industrial or consumer needs but also these medical needs. During the 1960's, a new research area developed whose objectives were to provide knowledge of how polymers interact as they interface with living systems, so that biomedical polymers can be developed in their own right. This research requires the coupling of many traditional disciplines as well as creating new interdisciplinary studies.

2. The Artificial Heart

The area that I have found most fascinating is the use of polymers in the repair of the vascular system and in the extracorporeal handling of blood. In the present paper this work will be described, using the artificial heart as the background for my remarks.

For some time, the Division of Artificial Organs, under the direction of *W. J. Kolff*, has been developing artificial heart devices. Much of this work has been concerned with a Kwan-Gett hemispherical heart[2] (cf. Figs. 1 and 2) and the development of optimum surgical procedures as well as pre- and post-operative care techniques. Considerable progress has been made, as indicated by the world's record time of two weeks which a calf has remained alive after implantation of an artificial heart.

However, there are still problems such as: occasional mechanical failure, poor fit, inadequate pumping, improper blood pumping pressure, need for improved valves, *etc.* Also, we

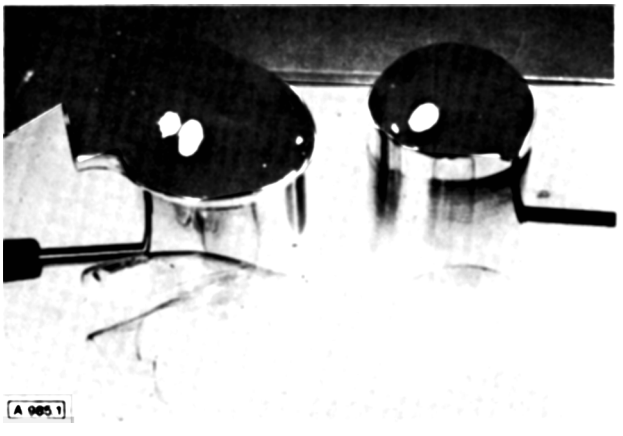


Fig. 1. The molds, fabricated copolyurethane housing, and diaphragm for a Kwan-Gett hemispherical heart.

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Fig. 2. Kwan-Gett hemispherical heart (right ventricle) just prior to implantation (cf. Ref. [3]).

still do not have an ideal material to interface with the blood. As a result we find clots on the surface of the artificial heart, and there is evidence that these clots break loose and can lead to emboli and subsequent damage to distant tissues (cf. Fig. 3). The cellular elements such as red blood cells and

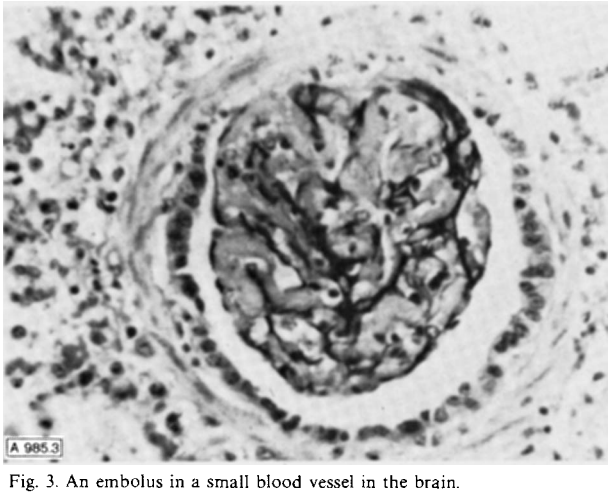


Fig. 3. An embolus in a small blood vessel in the brain.

platelets are damaged and destroyed (cf. Fig. 4). The protein constituents are also damaged. While these studies give an overall picture of the effect of the material on blood, there are two factors that must be kept in mind: 1. The animals

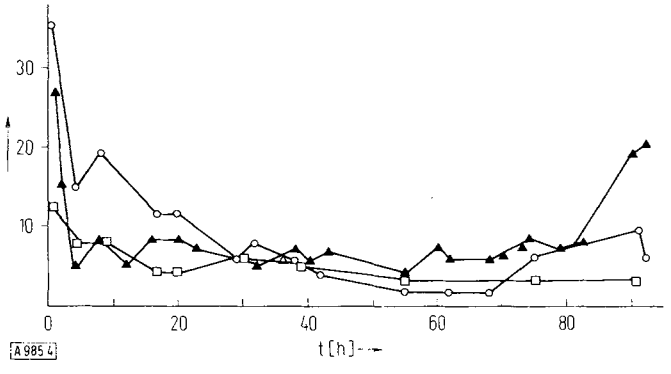


Fig. 4. Changes in the blood of a calf after implantation of an artificial heart. □ : plasmahemoglobin [mg/100 g], ▲ : clotting time [min], ○ : red blood corpuscles [10^4/cm^3].

own defense mechanisms can often clear the damage, thus masking a potential effect; 2. The tests, in themselves, give no clues as to the initiating steps in this damage.

We developed[4] a simple *ex-vivo* test which allows us to look more closely at this problem. If blood is allowed to flow over a polyvinyl chloride surface for several minutes in the absence of an air interface, a clot is formed (cf. Figure 5). On the surface of the plastic a thrombocyte can be seen

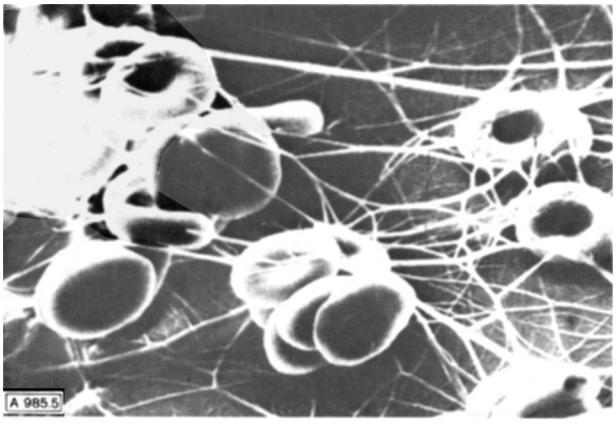


Fig. 5. Scanning electron microscope picture of a clot formed on a polyvinyl chloride surface in a flow-through *ex-vivo* cell showing platelets on the surface of the material and the fibrin mesh entrapping red blood cells. (Picture by *Rodman*, University of Iowa.)

with fibrin strands extending from its pseudopods. This fibrous mesh entraps red blood cells. However, while this has been valuable for guiding research and for screening polymers[4, 5], it still does not explain why the platelets adhere, and to what surface they are actually adhering. Our work has been directed toward answering these questions as well as the related one of how does one synthesize a non-thrombogenic polymer. This requires developing knowledge of the events occurring at the molecular level as the blood comes into contact with the polymer which initiate these adverse reactions. To do this, one must use model experiments (*in-vitro* and *ex-vivo*) to isolate and study the individual events that *might* occur at the molecular level in the *in-vivo* situation.

3. The Adsorption of Proteins on Polymer Surfaces

3.1. General

Blood coagulation has been studied for over 100 years, with many studies being directed toward identification of the activating molecule. These studies reached a high point in 1964 with the proposal of an enzymatic cascade blood clotting mechanism[6] resulting from surface contact of a particular protein molecule.

Our studies began here; on how proteins are adsorbed and activated on polymer surfaces. One tool that we have used extensively in this work has been infrared multiple internal reflectance spectroscopy. This method allowed us to examine directly the adsorbed protein-polymer substrate complex, without having to rely on indirect methods to estimate the interaction. Since both the infrared absorption of the adsorbed protein and the polymer appear in the spectrum (cf. Fig.

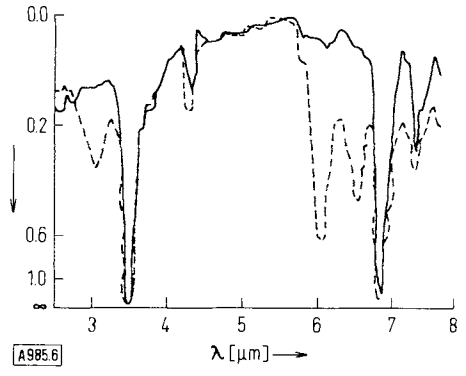


Fig. 6. IR multiple internal reflectance spectra of polyethylene (——) and γ-globulin (– – –) adsorbed on polyethylene.

6) one can use band ratios to determine the quantity of protein adsorbed[7] and the rates of adsorption[8].

We studied the adsorption of the more common blood proteins on a variety of neutral, hydrophobic polymers. Experiments were done in the absence of an air interface under both static and flow adsorption conditions. Figures 7 and 8 show typical

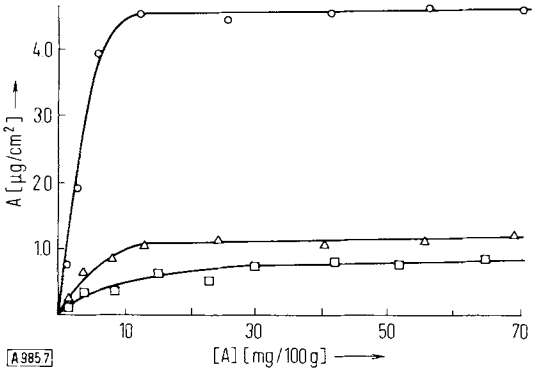


Fig. 7. Adsorption isotherms of albumin on various polymer surfaces: ○: copolyether-urethane-urea (PEUU-1), △: silastic rubber, □: fluorinated ethylene-propylene copolymer. Ordinate: A = amount of albumin adsorbed; Abscissa: albumin concentration in the solution in which the copolymer is dipped.

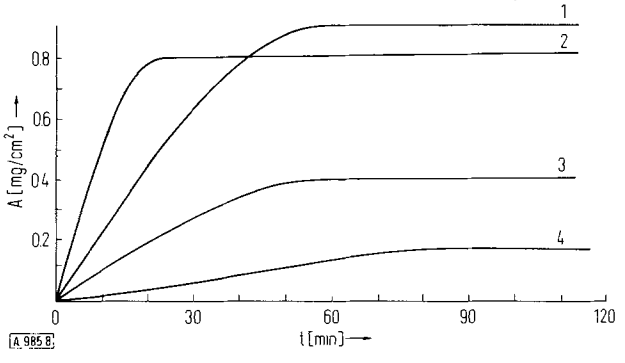


Fig. 8. Adsorption of various proteins on a fluorinated ethylene-propylene copolymer (after Ref. [22]). Ordinate: A = amounts adsorbed. 1: γ-globulin, 2: prothrombin, 3: albumin, 4: fibrinogen.

adsorption curves. It soon became apparent that the proteins were physically and essentially irreversibly adsorbed onto these neutral hydrophobic polymers with formation of a type of monomolecular layer. Electron micrographs and infrared spectra data (no shifts in Amide I—Amide II bands) would indicate that no gross structural alterations occur, *i.e.* the adsorbed proteins retain their globular form. As these studies continued we began to find differences in rates of adsorption, plateau concentration, effect of flow velocity on the amount of adsorbed protein, *etc.*, as we varied the adsorbing protein on the polymer surface.

At this stage, the *in vivo* experiments involving implanted cannulas that we were carrying out concurrently with the help of *William Edmark* (Providence Hospital, Seattle), began to influence our thinking. On all of the surfaces examined by us, a platelet plug appeared to be at the site of clot initiation. In many cases, the total clot appeared to be an aggregated platelet mass. On considering these contrasting sets of experiments, I began to feel that there was an overemphasis on "contact surface activation" by the Hageman factor (Factor XII) and that the mechanism on the implanted polymer surface might more nearly resemble what happens when the natural vessel wall is cut.

We began, therefore, to study the adhesion of platelets to various polymer surfaces. In the beginning, we simply dipped films into blood, then rinsed and stained the surfaces. All the surfaces had large numbers of platelets on them, and all appeared surprisingly similar. However, since it was known that proteins denature at an air interface and it was possible that we were simply coating our polymer with denatured protein by the dipping—essentially a Langmuir transfer of protein to the surface—we redesigned our system to avoid an air interface.

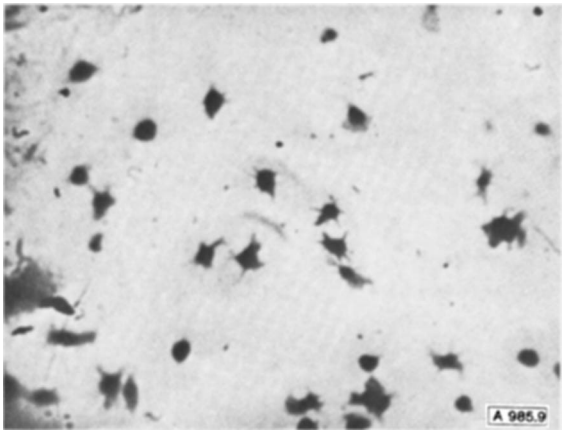


Fig. 9. Stained platelets adhering to a fluorinated ethylene/propylene copolymer surface after exposure in our flow-through *ex-vivo* cell (after Ref. [4]).

The flow-through cell was simply a small glass chamber to which we could clamp the polymer films to be examined and which could be filled with buffered saline. Human venous blood is introduced directly (*via* a vena puncture) to the cell, thus displacing the original salt solution. Care must be taken to avoid air bubbles. The cell is then quickly rinsed and the adsorbed platelets fixed and stained. On some surfaces, pseudopod development could actually be observed (see Fig. 9). If the blood is exposed for longer times, an actual clot resembling that shown earlier in Figure 5 is formed.

As we examined a series of neutral hydrophobic polymers under these conditions and compared the number of platelets adhering at one minute exposure, we were able to establish

that the number of platelets is greater, the more thrombogenic the plastic material is[4]. At longer times of exposure, all surfaces begin to look rather similar. This is not unexpected, since all are considered thrombogenic, the only difference being in how long they take to clot[3, 9, 10].

3.2. The Passivation of Polymer Surfaces

Since our protein adsorption studies indicated that a polymer surface could be coated with a layer of protein without altering the protein structure, we explored the possibility of passifying a polymer by pre-coating it with albumin. Indeed, when we tested such pre-albuminated surfaces in our flow-through platelet test cell, we found essentially no platelet adhesion[11]. If our hypothesis is true, this albuminated surface should be non-thrombogenic. *Lande*, who used albuminated membranes in an artificial lung[12], was also able to detect markedly reduced platelet damage. Later, *Andrade* prepared covalently bonded albumin surfaces on Gott vena-cava rings[13]. These were shown to be as non-thrombogenic as heparinized surfaces[5]. Hence, if we could avoid platelets adhering to a surface we should be able to avoid the formation of a clot.

In view of our interest in materials for artificial heart devices, we began to explore a variety of segmented copolyether-urethanes and urethane-ureas for possible candidates. In this polymer family the mechanical properties can be tailored to meet great variety of requirements. One of these polymers, a copolymer based on polypropylene glycol, 4,4'-methylene(diphenyl isocyanate) and ethylenediamine appears to have a fair balance of mechanical and fabricating properties. Examination of this copolyether-urethane-urea in our platelet cell gave surprising results: it showed very low platelet adhesion[15]. Also, when Gott rings were implanted in the inferior vena cava of dogs, they were proved to be as non-thrombogenic as rings with heparinized surfaces[14].

We carried out some preliminary studies on implanting a polyurethane hemispherical Kwan-Gett heart[3]. Although we did not achieve long survival times with these initial implantations, the heart, on removal, was as clean and shiny as when implanted. There was no evidence of clots, fibrin deposition or platelet deposits anywhere in the heart. Because of the heavy scheduling of other types of hearts, and other surfaces such as fibril coated surfaces[*], we shifted our efforts back to gaining an understanding of how these two types of non-thrombogenic surfaces function. What are the similarities and differences between an albumin coated surface and a segmented copolyether-urethane-urea surface? Since precoating a polymer surface with albumin passifies the surface and prevents platelet adhesion, can this same effect be achieved *in situ;* in other words, can the urethane surface preferentially and rapidly adsorb albumin from the blood?

On examining the nature of protein adsorption onto polymer surfaces in more detail[8], data supporting this hypothesis began to emerge. In the series of polymer surfaces examined, those having higher rates of albumin adsorption and also having higher plateau concentrations of albumin on the surface were less thrombogenic. There also appeared to be an inverse relationship for γ-globulin adsorption, *i. e.* the more γ-globulin on the surface, the more thrombogenic the polymer appeared to be.

It is assumed, of course, that adsorptions occurring in a mixture, *e. g.* whole blood, are similar to those observed in a simple, single solute. This is currently being checked. However, this assumption is supported by our platelet adhesion studies which show that both γ-globulin coated surfaces and fibrinogen coated surfaces are more active toward platelets[8] than are albumin surfaces. It is also supported by the work of other investigators[17, 18] which shows the adverse effects of γ-globulin on platelet adhesion and release reactions. Thus it would appear that the way to achieve a non-thrombogenic surface is to either pre-coat the polymer with a passifying layer of albumin or have a polymer of such a chemical structure that it forms this passifying albumin coating rapidly *in situ.*

Our work is currently proceeding along several lines involving: 1. Investigations on the nature of the protein-polymer interaction; 2. Determination of the actual chemical and inherent water structure of the proteinated surfaces; and 3. Determination of the nature of the platelet-protein surface interaction. These studies will allow us to develop much of the basic knowledge of blood interactions with polymeric surfaces; knowledge which is necessary if we are to advance the repair of the vascular system and the extracorporeal treatment of blood.

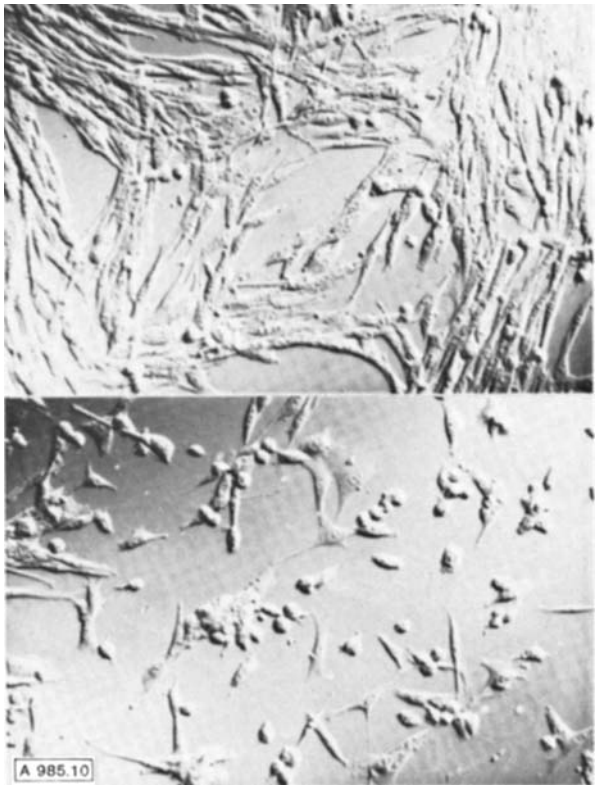


Fig. 10. Cell culturing of baby hamster kidney cells. Top: onto glass, showing adhesion and growth. Below: onto a polyurethane surface, showing no growth.

Recently, there has been increased interest in cell culturing on surfaces as an alternate method of passivation[19]. The neo-intima which develops provides a natural surface to the blood. However, lack of cellular adhesion to the Silastic

[*] It should be noted that, after much implantation and post-operative study, the world's record long-term survival was achieved by the Division of Artificial Organs using a fiber coated surface [16].

Rubber substrate has necessitated the use of Dacron fiber-coated surfaces to prevent the cellular deposits from being stripped off. This, of course, is not without its own problems. Therefore, *Hill* and I investigated the adhesion of baby hamster kidney (BHK-21) cells[20] to polymer surfaces. Normally, if the BHK-21 cell adheres, it will grow to form a monolayer; if it does not adhere, it will ball up and die (cf. Fig. 10). On examining a series of copolyether-urethane-ureas, which were chemically identical except for the length of the polyether segment, we noticed an interesting phenomenon[21]. When the polyether segment had a molecular weight of 400, 700, or 2000, the BHK-21 cells adhered and grew normally; when the polyether segment had a molecular weight of 1000, the cells did not adhere and grow. Parallel experiments on platelet adhesion showed the same result, *i.e.* platelet adhesion on the polymers whose polyether segments had molecular weights of 400, 700, or 2000, but no adsorption on the polymer whose polyether segment had a molecular weight of 1000.

These four types of copolymers showed similar critical surface tensions and protein adsorption. However, it must be kept in mind that these involve gross measurements, and that the cells are apparently capable of recognizing some microarchitectural differences in these copolymers. Indeed, preliminary studies on the tacticity of the polypropylene glycol segments and on the film morphology would indicate that the copolyether-urethane-urea containing the polyether segment with a molecular weight of 1000 is different from the others. We are now working on the determination of the structure of these surfaces and shall couple this information with our other blood studies.

These studies are of double interest to us. Platelets are rather difficult to handle, so if we do have a cell line that mimics their action we could do more quantitative studies on the nature of the polymer surface interaction. Also, if each cell line has its own surface recognition pattern, we might be able to make a surface that will preferentially adhere (and grow) one cell line in the presence of others. This would allow us then to develop scaffolding polymers to assist the body in the controlled repair of its own tissue and organs, whether it be a nerve, the trachea, or a blood vessel.

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German version: Angew. Chem. *86*, 145 (1974)

[1] *D. J. Lyman*, Rev. Macromol. Chem. *1*, 355 (1966).

[2] *C. Kwan-Gett, H. H. J. Zwart, A. C. Kralios, T. Kessler, K. Backman*, and *W. J. Kolff*, Trans. Amer. Soc. Artif. Intern. Organs *16*, 409 (1970).

[3] *D. J. Lyman, C. Kwan-Gett, H. H. H. J. Zwart, A. Bland, N. Eastwood, J. Kawai*, and *W. J. Kolff*, Trans. Amer. Soc. Artif. Intern. Organs *17*, 456 (1971).

[4] *D. J. Lyman, K. G. Klein, J. L. Brash*, and *B. K. Fritzinger*, Thromb. Diath. Haemorrh. *23*, 120 (1970).

[5] *D. J. Lyman, K. G. Klein, J. L. Brash, B. K. Fritzinger, J. D. Andrade*, and *F. S. Bonamo*, Thromb. Diath. Haemorrh. Suppl. *42*, 109 (1970).

[6] *R. G. Mac Farlane*, Nature *202*, 498 (1964).

[7] *J. L. Brash* and *D. J. Lyman*, J. Biomed. Mater. Res. *3*, 175 (1969).

[8] *S. W. Kim, R. G. Lee*, and *D. J. Lyman*, unpublished.

[9] *L. I. Friedman, H. Lien, E. F. Grabowski, E. F. Leonard*, and *C. W. McCord*, Trans. Amer. Soc. Artif. Intern. Organs *16*, 63 (1970).

[10] *D. J. Lyman*, Trans. Amer. Soc. Artif. Intern. Organs *16*, 75 (1970).

[11] Chem. Eng. News *47*, No. 4, p. 37 (1969).

[12] *A. J. Lande, L. Edwards, J. H. Bloch, R. G. Carlson, V. Subramanian, R. S. Aseheim, S. Scheidt, S. Filmore, T. Killip*, and *C. W. Lillehei*, Trans. Amer. Soc. Artif. Intern. Organs *16*, 352 (1970).

[13] *V. L. Gott* and *A. Furuse*, Fed. Proc. *30*, 1679 (1971).

[14] *V. L. Gott, M. D. Ramor, F. B. Najjar, J. C. Allen*, and *K. E. Becker* in *R. J. Heggeli*: Proceedings of Artificial Heart Program Conference. U. S. Govt. Printing Office, Washington 1969, p. 151.

[15] *D. J. Lyman, J. L. Brash*, and *K. G. Klein* in *R. J. Heggeli*: Proceedings of the Artificial Heart Program Conference. U. S. Govt. Printing Office, Washington 1969, p. 113.

[16] *E. J. Hershgold, C. J. Kwan-Gett, J. Kawai*, and *K. Rowley*, Trans. Amer. Soc. Artif. Intern. Organs *18*, 181 (1972).

[17] *M. F. Glynn, M. A. Packham, J. Hirsh*, and *J. F. Mustard*, J. Clin. Invest. *45*, 1013 (1966).

[18] *J. F. Mustard, M. F. Glynn, E. E. Nishizawa*, and *M. A. Packham*, Fed. Proc. *26*, 106 (1967).

[19] *C. G. LaFarge* and *W. F. Bernhard* in *R. J. Heggeli*: Proceedings of the Artificial Heart Program Conference. U. S. Govt. Printing Office, Washington 1969, p. 619.

[20] *J. C. Taylor, D. W. Hill*, and *M. Rogalsky*, Exp. Cell. Res., in press.

[21] *D. J. Lyman, D. W. Hill, R. K. Stirk, C. Adamson*, and *B. R. Mooney*, Trans. Amer. Soc. Artif. Intern. Organs *18*, 19 (1972).

[22] *J. Hamburger, J. Crosnier*, and *M. H. Maxwell*: Advances in Nephrology (From the Necker Hospital), Year Book Medical Publishers, Chicago 1972, Vol. 2, p. 96.

Structure-Property Relationships in a Polymer[**]

By E. H. Andrews[*]

The way in which polymer molecular structure controls structure on higher levels of organization in a solid polymer is briefly reviewed, as is also the way in which structure, on all levels, controls physical properties. The "line of descent" from molecular structure to physical properties is then illustrated for *cis*-polyisoprene (natural rubber). It is shown how the crystalline-amorphous morphology in the solid is controlled both by the chemical microstructure of the polymer and by the physical conditions (temperature, time, strain) under which solidification occurs. By changing these "processing conditions" great changes can be effected in the morphology.

1. The Role of Molecular Structure

This paper is not primarily concerned with molecular structure, but it is impossible to discuss "structure-property" relationships without beginning at this point. One of the main ideas behind this paper is that the molecular structure of a polymer does not uniquely define its solid-state properties and that the latter often depend much more strongly on the higher levels of structure ("morphology"). It must never be forgotten, however, that the morphology of a solid polymer itself derives

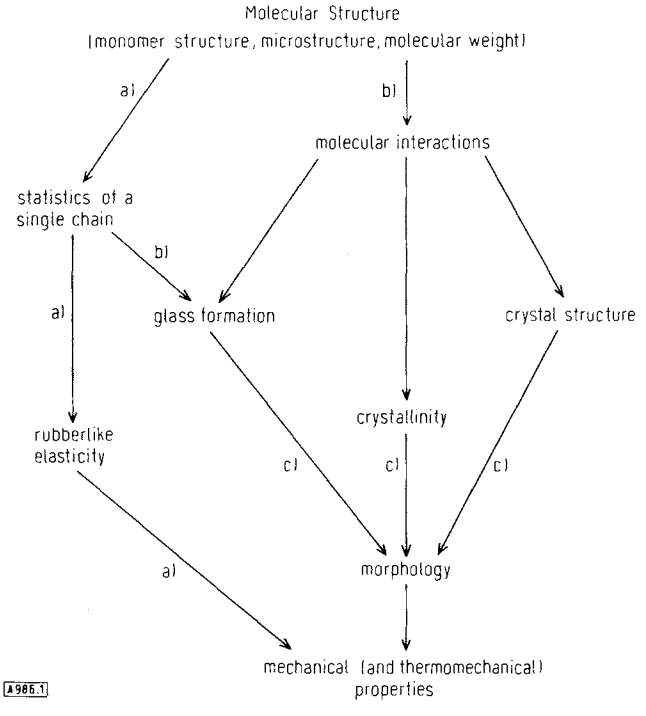


Fig. 1. Property-structure lines of descent (schematic).

from the "interaction" of the molecular characteristics with the conditions under which the morphology is formed. We have only to remember that polymers as materials are what they are because they possess a characteristic molecular structure, namely that of a long chain.

The proper perspective in structure-property relationships can best be given diagrammatically. In Figure 1 is shown a kind of "family tree" or line of descent, tracing the properties of polymers back to their molecular structure. To avoid overcomplicating the diagram, I have restricted it to the thermomechanical category of properties and omitted the electromagnetic and chemical property categories. Clearly, however, these aspects could be included in a similar manner.

Reference to Figure 1 reveals immediately the very complicated nature of the dependence of mechanical properties (including thermomechanical properties) upon molecular structure. This is why many early attempts to relate properties directly to molecular structure met with only limited success.

There is one property, that of rubberlike elasticity, which is largely dependent upon the independent behavior of single molecules (route (a) in Figure 1). This behavior is found at temperatures sufficiently high that the kinetic motion of the molecules swamps the constraint of molecular interactions. The material then behaves, to a first approximation, as an assembly of non-interacting chains.

All other mechanical properties, however, depend strongly on molecular interaction. Indeed the temperature range over which rubberlike behavior is observed is itself limited by the phenomenon of glass formation where molecular interactions predominate.

The role of interaction is indicated by routes (b) in Figure 1. According to the molecular structure, interactions result in the establishment of structures of a higher order, namely glasslike and crystal structures. Which of these two structures will form as a polymer is cooled from the melt or precipitated from solution depends both on the inherent capacity to crystallize and on the relative rates of cooling (or precipitation) and crystallization. Both capacity and kinetics are controlled by the molecular microstructure as well as by the more obvious thermodynamic parameters. Commonly both crystalline and amorphous regions occur in the solid polymer and their relative amounts and arrangements (size, shape, orientation, organization) depend not only upon the factors mentioned above but also on mechanical parameters such as stress or strain obtaining in the system during the formation of the morphology in Fig. 1c).

Finally, the mechanical properties are dependent directly on the morphology, since the response of the solid to stress or strain is the averaged sum of the responses of the individual components in the morphology. If the polymer is a homo-

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geneous glass, the "morphology" must be construed in terms of appropriate concepts such as free-volume, close-range order, and mean molecular orientation. If the polymer is a "composite" of crystalline and amorphous phases the situation is more complex, involving the totality of structural characteristics in both phases together with specific phase interactions (*e.g.* tie molecules anchored by the crystalline phase but extending through the amorphous phase).

It is clearly impossible to deal here with the whole area defined by Figure 1. In what follows, the kinds of dependence discussed above will be illustrated mainly by examples drawn from our experience over some years of a single polymer—*cis*-polyisoprene or natural rubber.

Apart from the importance of this material in the history of polymer science, there are additional advantages of working with polyisoprene. It can be readily and quantitatively isomerized to change its microstructure; it crystallizes sufficiently slowly to allow control of the morphology; it can be obtained in a wholly amorphous condition for comparison with semicrystalline specimens and, finally, the amorphous phase can be changed from glassy to rubberlike by passage through the glass transition temperature at the reasonably convenient temperature of $-70\,^{\circ}C$, without changing the crystalline phase in any way.

The examples chosen below to illustrate structure-property relationships are as follows. Firstly, the effect of small microstructural changes on the morphology and kinetics of crystallization. Secondly the effect of strain on morphology, strain being regarded as a "processing variable", and thirdly, the effect of morphology upon some high-strain mechanical properties such as modulus, yield stress, and fracture stress. The work is discussed here in review form only and further details will be found in the references.

2. The Effect of Molecular Microstructure on Crystalline Morphology and Kinetics

Final properties, we have asserted, depend on morphology and this, in turn, depends upon those kinetic processes which give rise to it. It follows that crystallization kinetics, interacting with the "processing conditions" (thermal history, for example) are of central importance to the subject. *Andrews*, *Owen*, and *Singh*[1] have investigated the effect of small changes in molecular microstructure upon the crystallization kinetics of *cis*-polyisoprene. The changes were of two kinds, namely small amounts (up to 10%) of isomerization of the initially *cis* polymer and chemical crosslinking by peroxide decomposition involving equally small numbers of monomer units.

The linear growth rates of lamellar crystals (grown in very thin films of the melt) were measured directly using electron microscopy and an osmium tetroxide staining technique which arrests crystal growth after any chosen period of time. The dramatic results are shown in Figure 2. At a given temperature ($-26\,^{\circ}C$) the linear growth rate, G, of the crystals is reduced one-thousand fold by the random introduction of one isomerized unit in ten homopolymer units (10% isomerization). There is a linear dependence of log G upon the fraction β of isomerized material. A similar effect is produced by crosslinking, although this appears to be only half as effective as isomerization in suppressing the crystal growth rate.

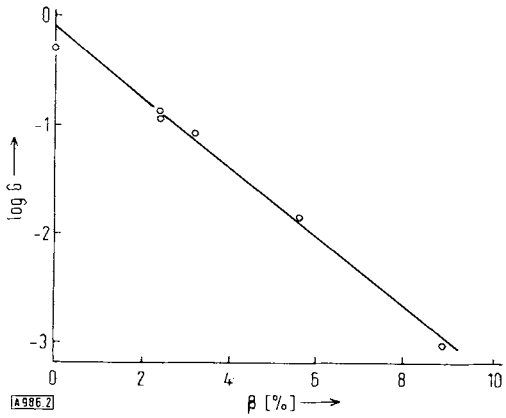


Fig. 2. Single crystal growth rate G (in μm/h) at $-26\,^{\circ}C$ as a function of the fraction β of *trans* isomer in *cis*-polyisoprene (after [1]).

Since the temperature dependence of G was unaffected by isomerization or crosslinking, it was concluded that the reduction in G could not be due to changes in the thermodynamic parameters (heat of fusion, melting temperature, interfacial energies) which appear in the classical equations[2] for growth by secondary nucleation. Instead, the authors explained their result in terms of a novel "exclusion" mechanism, as follows.

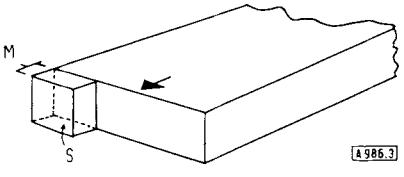


Fig. 3. Crystal growth by secondary nucleation (S) in the direction of the arrow. M = monolayer.

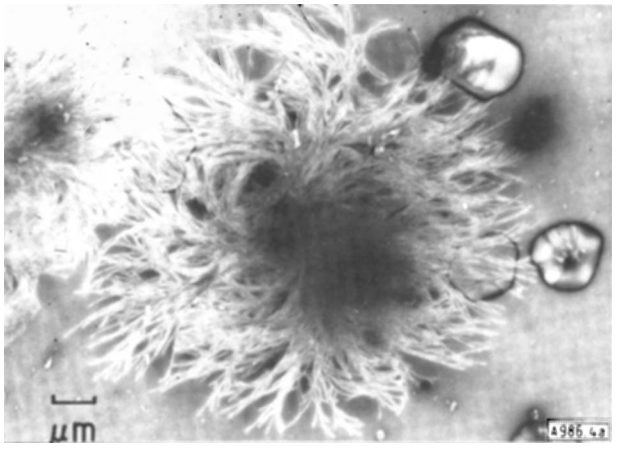
Continuous growth of a polymer crystal occurs by a modification of the classical "secondary nucleation" process. In this process, the slowest (and thus the rate controlling) step is the deposition of a new block of solid material on to a smooth growth surface (Fig. 3). Once this block (the "secondary nucleus") has been deposited, a new monolayer is rapidly completed because atoms or molecules crystallize readily at any step on the surface. In polymer crystallization the process is probably more complex, involving the secondary nucleation of each separate molecule on to the growth surface. In either case, however, it is necessary to establish a secondary nucleus which is large enough to be thermodynamically stable. This "critical size" requirement suggested that an uninterrupted sequence of homopolymer units, sufficient in number to form a critical size nucleus, was a requirement for the attachment of a new molecule to the growth surface. *Andrews et al.* were able to show theoretically that the crystal growth rate G would be affected by the fraction β of randomly distributed "foreign" units according to the equation

$$\ln(G/G_0) = -(N-1)\beta \qquad (1)$$

where G_0 is the growth rate for the homopolymer and N is the number of monomer units required in uninterrupted sequence. Not only does eq. (1) describe exactly the relationship found in Figure 2, but the value deduced for N gave a width for the secondary nucleus of 1.98 nm compared with an independent thermodynamic estimate of 1.94 nm.

It appears, then, that the growth kinetics are extremely sensitive to molecular imperfections of whatever kind, the effects being far more marked than those of molecular weight variation[3], for example. The amount and perfection of crystallinity achieved in a polymer subjected to a given processing history is thus likely to be equally sensitive unless care is taken to anneal the material.

The influence of small amounts of isomerization upon the ultimate (*i.e.* well annealed) morphology is negligible. Thus provided time is given for the crystals to grow to their full extent, the results are wholly similar. In normal polymer conversion processes, however, such as extrusion, fiber spinning, blow molding, *etc.*, morphology may be strongly affected by changes in crystal growth kinetics. For example, regions which crystallize under high shear stress will have a very different morphology from regions which crystallize after the shear stress has relaxed. Rapidly crystallizing species may thus have a "high shear" morphology due to transient shear stresses, whilst slowly crystallizing species may reveal little or no "memory" of the time spent by the melt under shear.



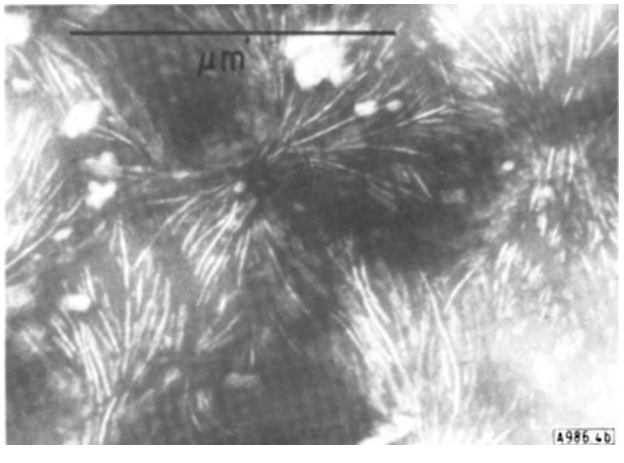
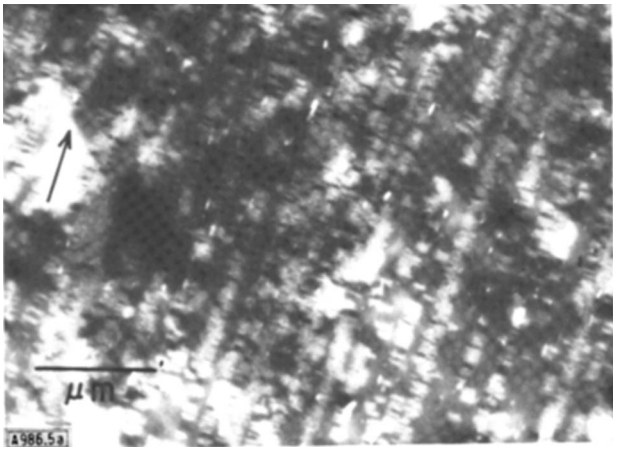


Fig. 4. a) Spherulite grown in a thin film of natural rubber (stained with OsO_4) (after [1]). b) As Fig. 4a, but in a film crosslinked by exposure to disulfur dichloride vapor (after [4]).

Crosslinked specimens of *cis*-polyisoprene, unlike isomerized material, *do* exhibit important morphological differences from the uncrosslinked case[4] (Fig. 4 and 5). Figure 4a shows a spherulite grown in an uncrosslinked thin film and Figure 4b one grown in a crosslinked film. In the latter, the lamellae are relatively short and discontinuous by comparison with



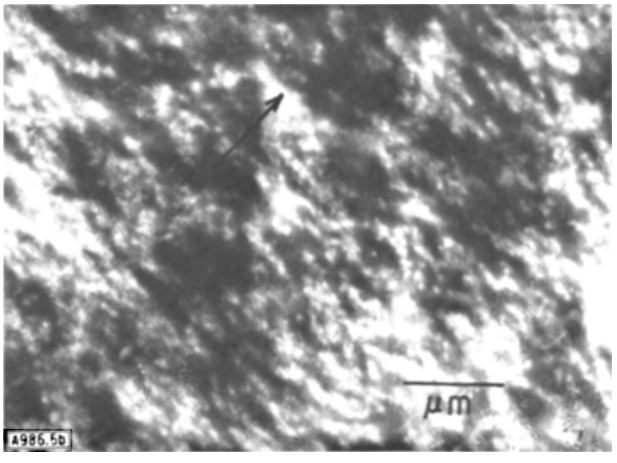


Fig. 5. a) Row nucleation in a thin film of natural rubber crystallized at 200% strain (stained with OsO_4) (after [4]). b) As Fig. 5a, but in a film crosslinked by disulfur dichloride vapor (after [4]).

the former. This may be due either to the physical impedance of growth by localized regions of high crosslinking or to an increased tendency for nucleation of lamellae resulting in a large population of "young" (and thus short) crystals. Figure 5a and b show a similar contrast for crystallization in a strained film (see Section 3.1). The long row-nucleated structures, often up to 10—20 µm, typical of uncrosslinked rubber are strongly suppressed by crosslinking. Row nuclei still occur in crosslinked specimens, but are typically only a fraction of a micron in length, though much more numerous. The explanation of this may at first appear to be a physical blockage of row-nucleus growth, but is more likely to arise from the increased elasticity of the melt (which opposes the shape change involved in the formation of a long cylindrical nucleus).

3. The Effect of Mechanical Constraint on Morphology

3.1. Strain in the Melt

During polymer conversion the melt is normally subject to deformation, either by shear in the die or mold, or by subsequent drawing or blowing processes. The degree to which these processes affect polymer morphology depends on the time, temperature, and the severity of the deformation. If the stresses relax before crystallization is initiated, the latter

occurs isotropically, but if stresses are present during even the early stages of solidification the effect on morphology can be profound.

Natural rubber films have a sufficiently high molecular weight to sustain applied stress in their melt condition even in the absence of crosslinking. They therefore afford a model thermoplastic system in which the effects of melt stress can be studied by the application of *static* strain (not possible in most polymer melts).

The results of this study are already well-documented[5], and Figures 4a and 5a have already been given to show the morphological differences between a film crystallized unstrained and one crystallized from a strained (200%) melt. Kinetic evidence[2] reveals that the stress relaxes rapidly in the strained (uncrosslinked) film, so that most of the crystallinity develops in a relaxed film. The *initial* crystallization, however, consisting of a row nucleus, forms rapidly under stress and governs the subsequent growth morphology even after the stresses have relaxed.

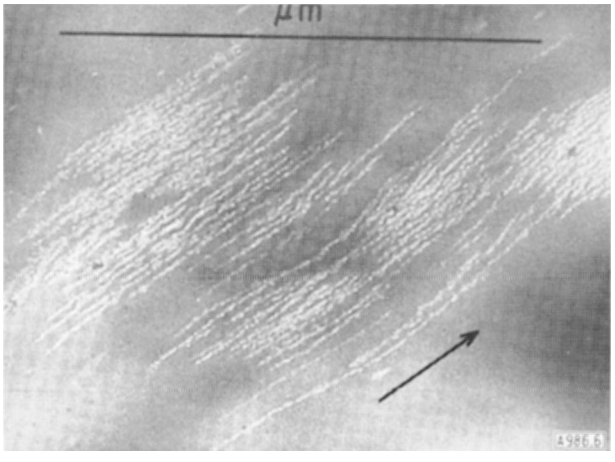


Fig. 6. γ-Filaments in thin film of natural rubber crystallized at 400% strain.

At higher melt strains the density of row-nucleation increases, and the crystal melting temperature is elevated until spontaneous crystallization occurs at room temperature in a form described by *Andrews*[5] as γ-filaments (Fig. 6). Alongside the

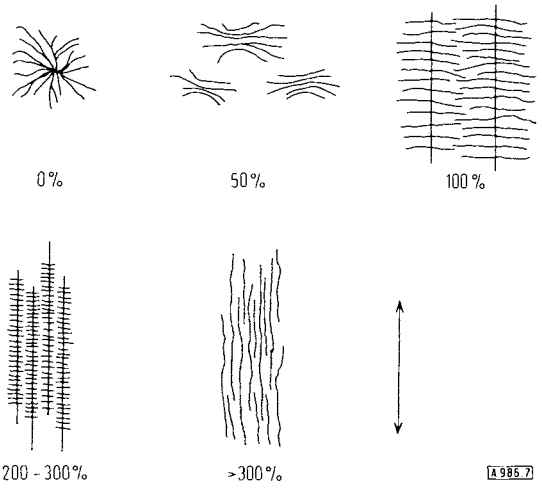


Fig. 7. Morphological effects of melt strain (direction of arrow) in crystallized natural rubber (schematic).

obvious morphological changes associated with crystallization from a strained melt must be included the hidden morphological variable of molecular orientation in the amorphous phase. Figure 7 summarizes schematically the morphological effects of melt strain in natural rubber. In all cases the molecular chain axis is normal to the plane of lamellar crystals but lies parallel to the length of row nuclei and γ-filaments. This encourages the view that the lamellae are essentially similar to the folded-chain single crystals obtained by precipitation from dilute solution, and the variation in their thickness with crystallization temperature[2] reinforces this view.

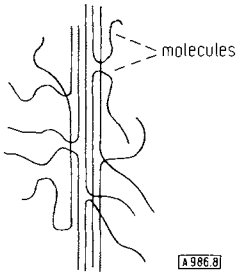


Fig. 8. Possible structure of row nuclei and γ-filaments (schematic).

In the same way, row nuclei and γ-filaments are probably highly imperfect extended chain crystals as sketched in Figure 8. The row nuclei formed at intermediate strains (Fig. 9 shows

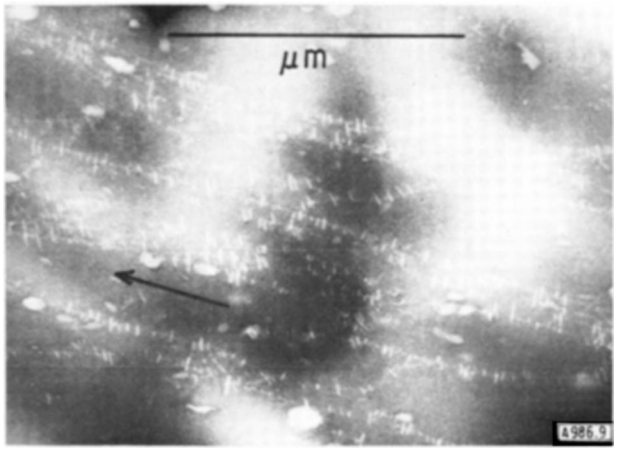


Fig. 9. Early stages of row-nucleated crystallization showing row nucleus.

the early stages) are often very cleanly defined filaments of diameter as little as 3 nm. By contrast, γ-filaments are always particulate along their length[5, 6] (Fig. 6). This difference may well arise because the γ-filaments form very rapidly (almost spontaneously) whereas the rate of growth of row-nuclei at lower strains (although greater than that of lamellar crystals by a factor of 10^2) is still measurable[4] at some 100 µm/h. The degree of perfection is thus much lower in the γ-filaments.

The qualitative features outlined in Figure 7 are not restricted to *cis*-polyisoprene, but appear to be quite general for the melt crystallization of thermoplastics. Thus almost identical patterns of behavior have been found for isotactic polymethyl methacrylate, polycarbonate[7], *trans*-polyisoprene[8], *trans*-polychloroprene, isotactic polystyrene[9, 10], and polyethylene[3].

The quantitative aspects of row-nucleated morphology depend, of course, upon the amount of row-nucleated material formed, since the row-nucleation density increases with time to a certain level and then remains constant. The final row-nucleation density has been measured[4] for *cis*-polyisoprene as a function of strain and temperature and is shown in Figure 10. The effect of strain is self-evident, but the effect of temperature is very interesting. As the melt becomes warmer the row-nucleation density first decreases to a minimum around -12 °C and then rises again. At high strains this rise is dramatic and clearly foreshadows the spontaneous γ-crystallization observed at slightly higher strains and temperatures.

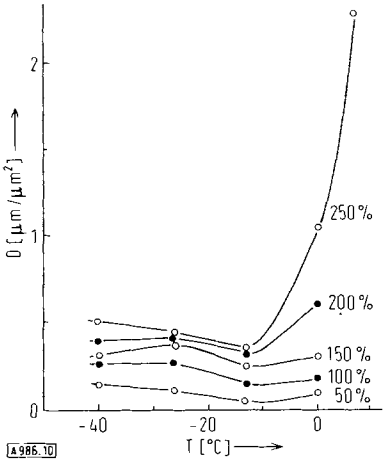


Fig. 10. Final row-nucleation density D for *cis*-polyisoprene as a function of strain (given alongside the curves) and temperature (after [4]).

3.2. Hydrostatic Pressure

Finally in this section we refer to a different mechanical constraint which can be imposed upon the melt during crystallization, namely that of hydrostatic pressure. It has been established that, in linear polyethylene, crystallization under high

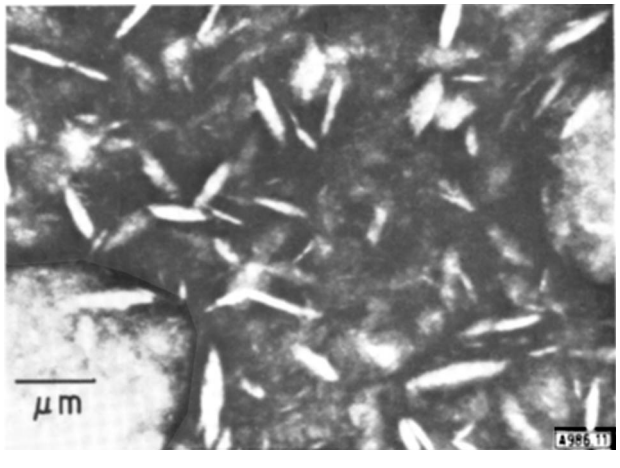


Fig. 11. Thin film of natural rubber crystallized at 20 °C at 4 kbar (after [13]).

pressure gives rise to a thickening of the normal folded-chain lamellae from a few hundred angstroms to several microns[11, 12]. The thickening at sufficiently high pressures and temperatures is such that the molecules unfold completely into an extended chain form. Material in this condition is extremely friable, *i.e.* has no mechanical strength, emphasizing the importance of intercrystalline amorphous material in imparting the toughness usually associated with polyethylene.

Some preliminary experiments[13] have been carried out on the crystallization of thin films of natural rubber under gas pressures of up to 5 kbar. The most obvious effects are that the nucleation density is vastly increased so that unstrained films no longer exhibit a spherulitic habit but, instead, show a high concentration of separate single crystal zones shaped like oblate spheroids (Fig. 11). Since there is good evidence[14, 15] that the "aspect ratio" (length-to-thickness ratio) of lamellae in a bulk polymer strongly affects its elastic modulus, the destruction of the spherulitic habit by pressure could significantly affect mechanical properties. Needless to say, many polymer forming processes involve the application of hydrostatic pressure as well as shear stress.

4. Morphology and Mechanical Properties in Natural Rubber

4.1. The Investigation

The investigations[16] detailed in this section, and carried out by *P. E. Reed*, were based on the thin film studies described in Section 3.2. Bulk specimens of lightly crosslinked natural rubber were crystallized at -26 °C under tensile strains ranging from 0 to 6 to develop the whole range of morphologies revealed by the thin film work. Crystallization was taken to completion in all cases giving a crystalline fraction of 0.3 ± 0.05 for all samples, and tensile tests were carried out at temperatures below -26 °C covering both the rubberlike and glassy regions of the amorphous polymer (above and below -70 °C respectively). From the stress-strain curves, mechanical parameters such as initial modulus, yield stress, fracture stress, and fracture strain could be obtained.

Basic to this work is the assumption that the morphology in bulk is essentially similar to that in thin films for equivalent melt strains, apart from the "three-dimensional" character of the former. Thus at zero melt strain we expect a spherulitic structure, at 50—100% spherulites flattened to bring their lamellar plane normals (molecular axis) towards the strain axis, at 100—400% cylindrical row-nucleated "shish-kebab" structures and at strains greater than 400%, γ-filaments. Because both lamellae and row nuclei are such small structures, thin sectioning of the bulk fails to reveal anything but a loss of spherulitic morphology with increasing strain. However, both light scattering[17] and X-ray[6] studies (of polychloroprene) provide strong indirect evidence that bulk morphologies correspond closely to their thin film counterparts at equivalent melt strain.

Reed's collected data for the mechanical properties of crystalline natural rubber is shown in a series of 3-dimensional graphs, Figures 12 to 16. Each diagram shows one mechanical property (*e.g.* fracture stress) plotted vertically as a function of pre-strain (*i.e.* melt strain, the "morphological variable") and of the temperature of testing. The results will be discussed separately.

4.2. The Initial Modulus

The initial tangent modulus to the stress-strain curve is shown for crystallized specimens in Figure 12. Spherulitic material (corresponding to pre-extension of 0% strain or extension ratio of unity) deforms in an essentially rubberlike manner above −60 °C, although its modulus is an order of magnitude greater than that of noncrystalline material. (On the scale of Figure 12 both these moduli are of negligible magnitude.) There is evidence from other sources[15] that the moduli of spherulitic polymers are strongly affected by detailed spherulite structure such as the lamellar aspect-ratio referred to earlier. The morphological evidence (Fig. 4b) thus suggests that crosslinked rubber, with discontinuous lamellae, should have a significantly lower modulus in the spherulitic form than uncrosslinked material. This accords with the observation that raw rubber increases its stiffness by at least two orders of magnitude when crystallized spherulitically compared with the tenfold change found here.

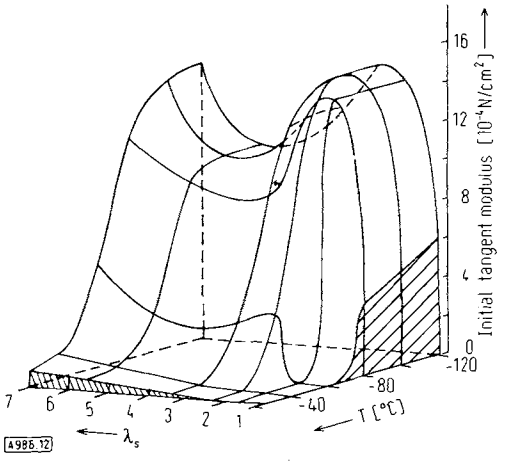


Fig. 12. Initial tangent modulus of crystallized natural rubber as a function of pre-strain and temperature. Yield surface shown plain, brittle fracture surface shaded (after [16]).

As the pre-extension increases, the morphology changes from spherulitic to row-nucleated and finally to γ-filaments, but the progressive rise in initial modulus above −40 °C can be attributed almost wholly to the increased orientation of the amorphous phase.

At an intermediate temperature of, say −60 °C, the effect of changing morphology is more dramatic, the modulus rising very sharply on the establishment of row-nucleated structures in place of spherulites, but thereafter remaining fairly constant. It is suggested[18] that this is due to a "fiber-reinforcement" mechanism in which the "shish-kebabs" act like oriented stiff fibers embedded in soft matrix. The effect fails to manifest itself at higher temperatures because the amorphous matrix is too soft, and fails to transmit significant shear stress from one "fiber" to another (this stress transmission is important because the fibers are discontinuous). At −60 °C the amorphous material is entering its glass transition range and losing its rubbery character.

Once the amorphous phase is fully glasslike (below −80 °C), the dependence of modulus on morphology follows a pattern which is not greatly affected by further reduction in temperature. The glassy state modulus of spherulitic polymer increases only twofold as the morphology is transformed to a row-nucleated form. That this increase can be attributed wholly to amorphous orientation has been convincingly demonstrated by studies on polychloroprene[6]. Clearly the elastic constants of the glassy and crystalline phases are now sufficiently alike for no "fiber reinforcement" to be observed. What is observed, however, is a wholly unexpected *decrease* in modulus with the establishment of the row-nucleated morphology above 100% pre-strain. This could be due to any of three causes. Firstly *Reed*[16] has shown that crystallization, under constant strain, into a row-nucleated morphology results in a relaxation of molecular orientation in the amorphous regions between lamellae. The *amorphous* orientation thus actually decreases with increasing pre-strain during the establishment of row-nucleated morphologies. This would reverse the trend observed for small pre-orientations, but would not really explain the persistence of the downturn in modulus up to high pre-extensions. Secondly, the lamellar orientation having now become uniformly transverse to the direction of testing, it could be argued that fiber reinforcement effects are minimized. *Reed*[16] found, however, that specimens tested at different angles to the direction of pre-extension showed very little difference in modulus at −120 °C, even when the angle was 90°. This shows that no "fiber reinforcement" occurs with lamellae in a glassy matrix as already proposed above.

Thirdly it is possible that the mutually aligned lamellae in row-nucleated structures are able to deform cooperatively by crystallographic mechanisms (*e.g.* [001] slip) to increase the compliance of the bulk. Until mutual alignment is achieved such deformations are relatively ineffective (*e.g.* in the randomness of the spherulite), but a stack of parallel crystals can deform "as one". Since the lamellae are reasonably extensive at intermediate pre-extensions they effectively separate the glassy matrix into "slices" perpendicular to the tensile axis, so that the matrix has relatively little ability to constrain the deforming crystals. As the row nuclei become more closely spaced with increasing pre-extension the horizontal continuity of the lamellar array diminishes and the matrix exerts a more effective constraint. This, together with the continuing rise in amorphous orientation, eventually causes the modulus to rise again at high pre-extensions.

This explanation of the dependence of modulus on morphology, although qualitative, is in reasonable accord with our present understanding of strengthening mechanisms in two-phase systems and opens the way to more quantitative investigations.

4.3. Yield and Brittle Fracture Stresses

In the glassy region, below −80 °C, the stress-strain curves of both crystallized and amorphous natural rubber exhibit either brittle fracture or yield followed by strain hardening, according to the temperature and pre-orientation. *Reed*'s data[16] for crystallized and amorphous rubber respectively are given in Figures 13 and 14. For pre-extensions above 300%, where spontaneous crystallization occurs during pre-extension, the data for the amorphous glass have been extrapolated algebraically. The regions of morphology and test temperature over which brittle fracture occurred are shown shaded. The testing rate was held constant throughout.

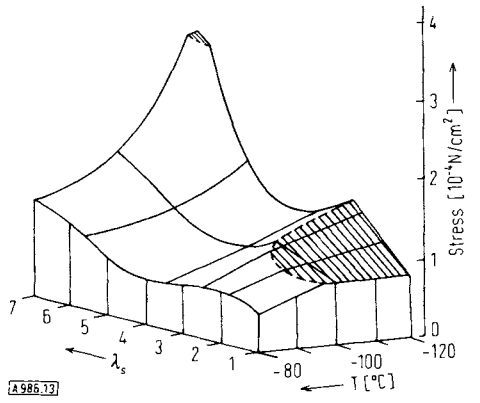


Fig. 13. As Fig. 12, but for yield and brittle fracture stresses of crystallized material (after [16]).

The differences between Figures 13 and 14 are not great, indicating that brittle fracture, yield, and strain hardening are all strongly affected by amorphous orientation in low

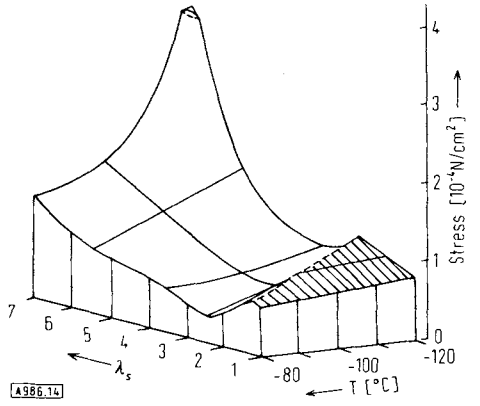


Fig. 14. As Fig. 13, but for amorphous material (after [16]).

crystallinity polymers. This is further borne out by studies[6] on polychloroprene at 18% crystallinity. At higher crystalline content, we have shown elsewhere[18] (for polyethylenes) that inter-lamellar attachments play a much stronger part in determining yield behavior.

Closer inspection of Figures 13 and 14 naturally reveals differences between the crystalline and amorphous cases. At low pre-extensions the brittle-ductile transition temperature is suppressed by the presence of crystallinity from -80 to about -95 °C. This is almost certainly due to the contribution of some low-stress ductility by the crystals. The second difference is that the shallow minimum which occurs in the yield stress as pre-extension increases, falls at a pre-extension ratio of 4 for the crystallized material but at 2.5 to 3.5 for the oriented amorphous specimens. This may again be explicable in terms of amorphous orientation since the local orientation in the amorphous phase of row-nucleated crystalline structures relaxes to a condition appropriate to a lower-than-nominal pre-extension (see Section 4.2).

If λ_s is the pre-extension ratio, *Reed*[16] calculated that the residual amorphous orientation in a row-nucleated specimen after crystallization would be

$$\lambda_{AR} = 4.41\lambda_s/(6.3 - 0.3\lambda_s)$$

which gives $\lambda_{AR}=3.5$ for $\lambda_s=4.0$ in good agreement with the shift of the minimum, at least at the lower temperatures. The occurrence of a minimum in yield stress thus appears to relate solely to amorphous orientation.

The third difference between amorphous and crystallized material is the rise in yield stress in the latter at large pre-extensions and low temperatures. This is perhaps directly attributable to the γ-filaments which we have suggested contain a large proportion of extended chain material. Whilst we have seen that crystals in a glassy matrix provide no reinforcement of modulus (because the elastic constants of the two phases are too similar), the λ-filaments *can* provide considerable strengthening when the glassy matrix begins to flow, providing of course, the γ-filament itself does not yield. This reinforcement-against-yield will be greater with γ-filaments than with lamellar structures because (a) [001] or chain-axis slip will be easier in the latter and (b) because gross tensile deformation causes buckling of lamellae and rapidly brings the [001] direction into the plane of maximum shear stress; in contrast, γ-filaments will not tend to reorient as a consequence of matrix flow.

It is likely that the yield phenomena discussed here are all associated with shear yielding. At lower temperatures *Reed* and *Natarajan*[19] have shown that a new mechanism of yielding (that of crazing) comes into play in natural rubber, and the competitive nature of these two yielding mechanisms has been widely recognized in glassy polymers[20].

4.4. Breaking Stress and Strain

Figures 15 and 16 show the breaking strain and stress respectively as functions of the usual variables for crystallized material. In the experiments, specimens are deformed in two stages, namely pre-extension to produce variable morphology and deformation during test. The variable of real significance is, of course, the total strain accommodated by the specimen before fracture and in Figure 15, therefore, is plotted this

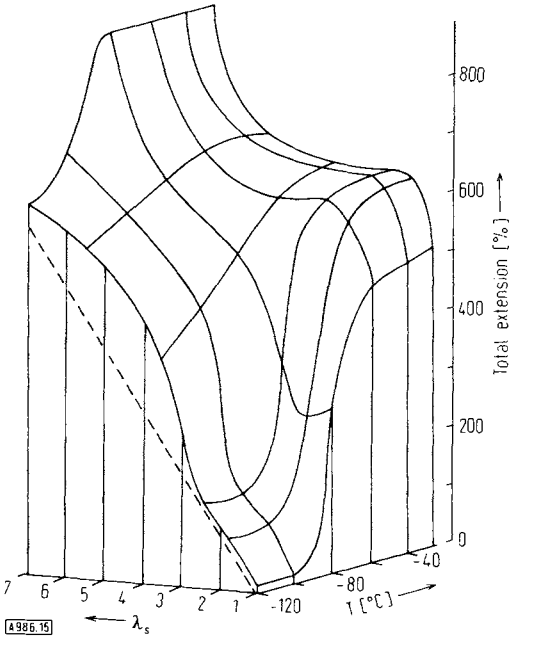


Fig. 15. As Fig. 12, but for total breaking strain. The broken line indicates the pre-strain (after [16]).

total strain given as the pre-extension plus the deformation during testing.

Plotted in this way it can be clearly seen that the fracture strain has a "plateau" value of some 600% over most of the experimental range except for two regions. The first of these is the region of brittle behavior already noted at low temperatures and low pre-extensions. Here very little extension occurs during test, the total strain deriving almost wholly from the room-temperature pre-extension. The second exception occurs at high pre-extension and temperatures above T_g where total extensions up to 900% are consistently recorded. This improvement in extensibility occurs with a morphology of γ-filaments in a rubberlike matrix and almost certainly results from a fiber strengthening mechanism which inhibits crack propagation normal to the fiber (γ-filament) axis. This mechanism is familiar in materials such as wood and arises from the relative weakness of inter-fibrillar bonds which encourages longitudinal fibrillation and blunts transverse cracks[21]. *Reed*[16] obtained striking fibrillation effects in specimens with very high pre-orientations.

Whilst the total extensibility of non-brittle specimens does not vary by a factor of more than 1.5 (and then only at high pre-extensions), the associated fracture stresses display drastic variations with morphological changes. This can be seen from Figure 16, where the load-bearing capacity nearly

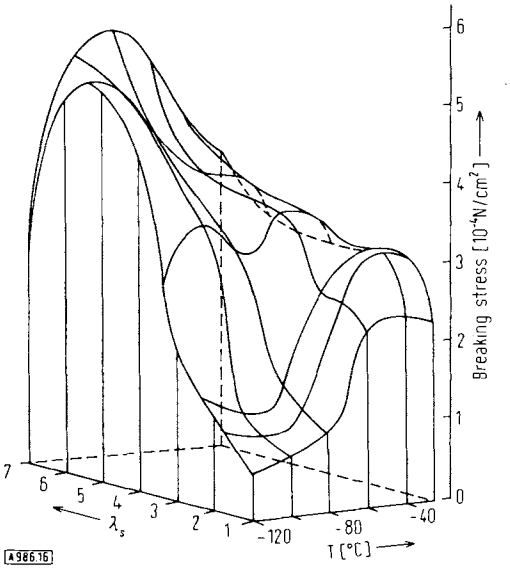


Fig. 16. As Fig. 12, but for true breaking stress. Changes in sample cross section accounted for (after [16]).

doubles at large pre-extensions as the temperature falls from −26 °C to −120 °C, and, at low temperatures, increases tenfold as the morphology changes from spherulitic to γ-filamentous. The breaking stress in Figure 16 is in all cases corrected for changes in specimen cross-section, *i.e.* it is the true load-bearing capacity of the material at the point of fracture.

At temperatures well above T_g, the breaking stress is fairly independent of pre-extension. Here the stress-strain curves are rubberlike and the morphology must undergo severe deformation before fracture. Since the actual fracture stress is independent of starting morphology, it is probably governed entirely by the amorphous matrix.

At low pre-extensions (up to $\lambda_s = 3$), the effect of reducing temperature through T_g is to produce embrittlement. Fracture here occurs in relatively poorly aligned material and the ultimate load-bearing capacity is understandably low. As pre-orientation increases, however, there is a rapid increase in the low temperature strength until (at $\lambda_s > 5$) reductions in temperature actually *increase* the strength of the material to a maximum before embrittlement once again causes a reduction. In the high strength region of Figure 16 the stress-strain curve, typically, exhibits yield and immediate, rapid strain hardening. As strain hardening becomes increasingly severe (with further reduction in temperature or increase in λ_s) the break in the stress-strain curve at yield is eliminated and brittleness again supervenes. This rapid strain hardening is typical of crystallized material and is not found in oriented amorphous polymers. It is thus attributable directly to the crystalline morphology.

The strength rise at −120 °C with initial pre-orientation is apparently associated with a rise in yield stress. Incipient yield appears to lead directly to fracture, and earlier these fractures were classified as brittle because there is no post-yield extension. Such a rise in yield stress can be attributed to amorphous orientation alone, although parallel tests on non-crystalline specimens showed that the latter always yielded at lower stress than the crystallized ones. Once yield is fully established, with significant post-yield deformation, the high breaking stress of the crystallized material is obviously a direct result of strain hardening which occurs far less rapidly in amorphous material. What is the cause of this strain hardening?

It has already been suggested that yield in the crystalline phase is progressively suppressed as lamellar or "shish-kebab" structures give way to extended-chain or γ-filament fibrillar morphologies. Since the yield stresses for amorphous and crystalline specimens are not very different in the intermediate range of pre-extensions, it seems likely that here, at low temperatures, the onset of yield is controlled by the glassy phase. As significant plastic deformation accumulates, however, the glassy phase can only continue to deform if the attached crystalline material also deforms to accommodate the change of shape. Whilst this is relatively easy for lamellar crystals, it becomes progressively more difficult as the crystalline phase assumes a fibrillar character. This mechanism has already been invoked to explain the rise in yield stress at high pre-extensions and extends naturally to the post-yield region. A further factor may be the increased amount of inter-fibrillar connection as the γ-filaments become more closely packed with increasing pre-extension.

Eventually the strain-hardening mechanism is self-defeating; the material becomes so inextensible that it becomes prey to weakening by flaws, lacking any plastic flow to blunt incipient cracks. A new brittle condition is thus established and the strength falls drastically at $\lambda_s > 6$.

5. Conclusion

The detailed discussion of *cis*-polyisoprene has illustrated the validity of the original proposition, namely that the properties of polymeric solids depend upon their structure at all levels and not solely upon their molecular structure. The complexity

of the data given in Figures 12—16 underlines the difficulty of providing simple rules in this area of structure-property relationships. Appeal has to be made to the anisotropic responses of both crystalline and amorphous phases to stress and, additionally, to specific mechanical interactions between the phases. It is in this latter area, for example, that molecular weight probably exercises a profound influence on mechanical behavior.

The work reported here, then, represents just a fraction of the painstaking task of "mapping" properties in the multidimensional reference frame of structure. It is only as we continue this mapping that a rational and consistent picture will emerge.

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[1] *E. H. Andrews, P. J. Owen,* and *A. Singh,* Proc. Royal Soc. (London) *A 324*, 79 (1971).

[2] *J. D. Hoffman* and *J. J. Weeks,* J. Chem. Phys. *37*, 1723 (1962).

[3] *J. M. Barrales-Rienda* and *J. M. G. Fatou,* Polymer *13*, 407 (1972).

[4] *P. J. Owen,* Ph. D. Thesis, University of London 1970.

[5] *E. H. Andrews,* Proc. Royal Soc. (London) *A 277*, 562 (1964).

[6] *E. H. Andrews* and *B. Reeve,* J. Mater. Sci. *6*, 547 (1971).

[7] *J. J. Klement* and *P. H. Geil,* J. Macromol. Sci. *B 6*, 31 (1972).

[8] *C. K. L. Davies* and *Ong Eng Long,* to be published.

[9] *A. Keller* and *M. J. Machin,* J. Macromol. Sci. *B 1*, 41 (1967).

[10] *G. S. Y. Yeh* and *S. L. Lambert,* J. Appl. Phys. *42*, 4614 (1971).

[11] *C. L. Gruner, B. Wunderlich,* and *R. C. Bopp,* J. Polym. Sci. *A 2*, 7, 2099 (1969).

[12] *D. C. Bassett* and *J. M. Phillips,* Polymer *12*, 730 (1971).

[13] *E. H. Andrews* and *P. J. Phillips,* J. Polym. Sci. *B 10*, 321 (1972).

[14] *J. C. Halpin* and *J. L. Kardos,* J. Appl. Phys. *43*, 2235 (1972).

[15] *P. J. Phillips* and *J. Patel,* personal communication.

[16] *P. E. Reed,* Ph. D. Thesis, University of London 1970.

[17] *W. Yau* and *R. S. Stein,* J. Polym. Sci. *A 2*, 6, 1 (1968).

[18] *E. H. Andrews,* Pure Appl. Chem. *31*, 91 (1972).

[19] *R. Natarajan* and *P. E. Reed,* J. Polym. Sci. *A 2*, *10*, 585 (1972).

[20] *P. Bowden* in *R. N. Haward:* The Physics of Glassy Plastics. Applied Science Publishers, Barking, Essex.

[21] *J. Cook* and *J. E. Gordon,* Proc. Royal Soc. (London) *A 282*, 508 (1964).

Biopolymers: Origin, Chemistry, and Biology

By Melvin Calvin[*]

A brief statement concerning the way in which biopolymers may have originated in the nonbiological world is made, including experimental evidence. This also includes a discussion of such matters as the way in which the code might have originated, that is, the relationship between polypeptides and polynucleotides as well as the secondary and tertiary structure resulting from the primary structure determination. The importance of the interaction of biopolymers with lipids for the formation of limiting membranes, leading to the formation of cells and other self-organizing cellular type organelles, is discussed. Thus, the second critical physical-chemical problem for cellular organization, namely, the biopolymer-lipid interaction, is now coming under scrutiny, both in terms of synthetic systems as well as natural ones.

1. Introduction

The collection of ideas presented here was compiled over a period of several months into the form of a review article containing four separate but closely interrelated sections. The first section discusses the origin of biopolymers, particularly of proteins, including the chemistry which may be involved. The next section describes the secondary-, tertiary-, and quaternary-structures of biopolymers and the interaction between proteins and nucleic acids. This is followed by a section on the origin of the genetic code. The last section deals with the interaction between the proteins and lipids.

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Why has this particular sequence been chosen? Many of the phenomena (reactions) under discussion are actually extrapolations and modifications of reactions with which polymer chemists are familiar. However, there seems to be a kind of curtain separating the polymer chemist, whose background is oriented to the structure and synthesis of macromolecules of any kind and the determination of the basic principles involved, and the group that has grown up in biology and biochemistry and which has learned about the physical chemistry and the chemistry of the behavior of the kinds of biopolymers they deal with[1]. The biochemists have felt that these things are almost magic, and they believe new rules, or laws, or chemistry, may be required to understand in detail how the naturally-occurring biopolymers (proteins, nucleic acids, *etc.*) perform their function. There appears to be some "mystique" about this, so an attempt is made in the following article to outline some of the reasons for this "mystique", which is generally in the minds of those who grew up from the side of biology. The behavior of biopolymers is interpreted in terms which are thoroughly familiar and which may even

appear somewhat naive to the polymer chemist. It must be remembered, however, that most of the work discussed here is being carried out by people who are not polymer chemists, and that is why some of the material may seem obvious to those of you who happen to be polymer chemists. Some of it, however, may not be obvious to you and could possibly give you fresh ideas for your line of research.

2. Formation of Biopolymers, Particularly Proteins

Let us begin with a consideration of the general scheme by which the two major biopolymers are constructed by living organisms. These are the proteins and the nucleic acids, and a sequence is shown schematically in Figure 1, beginning

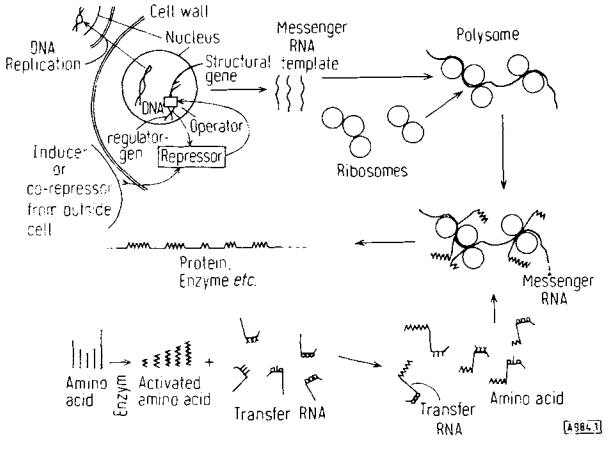


Fig. 1. Protein biosynthesis.

with the DNA double helix of the cell which can in some way (which is still not clarified) reproduce itself. That is, it can copy a particular sequence of nucleotide monomers in some particular order, and make a complementary copy, giving rise to a double set.

In addition, there is another type of reaction which occurs inside the cell. Instead of copying the DNA into another DNA strand, part of the DNA (which is an enormously long polymer, made up of essentially four bases hooked together by ribose phosphate linkages) can be copied into a ribose phosphate polymer, with a series of slightly different bases but related to the initial sequence. That part which is so copied contains in it the "message" for a particular protein. That is why this type of material is called "messenger RNA". The messenger RNA then leaves the cell nucleus and thus becomes the message for constructing a particular protein. The message is contained in the sequence of bases in the polymer. As is known, it takes three of these bases to designate a particular amino acid. The particular "messages" are then hooked onto the catalysts, which are themselves made up partly of protein and partly of nucleic acid and some lipid substances.

The situation is now ripe to put together the amino acids into a peptide. In order to do this, the amino acids must be suitably prepared. Each one of the different length straight lines in Figure 1 represents a different amino acid. The zigzag line represents the amino acid, acylated with a phosphate residue (aminoacyl phosphate or aminoacyl adenylate). This is then handed over to a small piece of polymer (RNA) constructed of about 70—100 monomeric units, containing in it somewhere a certain triplet (three bases in a row) which is characteristic of a particular amino acid; this distinction is designated by the different symbols in Figure 1 (circles, lines, crosses, squares), representing a different sequence of the three bases. Thus, each activated amino acid is loaded onto the terminus of a specific small oligomer (small polymer of the order of 70—100 units). We now have the amino acid loaded onto a particular transfer RNA (tRNA) with a particular triplet of bases characteristic of that amino acid. These are now free to attach themselves to the messenger RNA, the attachment taking place at points in the messenger where the complementary base triplets are to be found. Thus the sequence of the amino acids which go into the polymer to make the polypeptide is established. The polypeptide, is then "zipped up" to construct the protein. Generally, the protein is itself a characteristic polypeptide, having a typical shape and structure, which will be discussed in Section 4.

All of these reactions—the copying reaction (replication), the transcription into RNA, the activation, the loading, and the zipping-up on the ribosomes—are dependent for their specificity in part at least on the proteins which are themselves thus made. This is a "chicken and an egg" problem, and it sets the stage for the next part of the discussion.

How did this reflexive system, which is represented schematically in Figure 1, arise? As chemists, we would like to see if chemistry could have designed such a system and put it together in just this way. This is, of course, what should be understood as the nonbiological origin of the polymers and of the genetic code. How could this relationship between particular triplets and particular amino acids come into being?

I believe this relationship is the result of chemistry and not, as some of the biologists believe, a "frozen accident". However, experimental evidence for this is, as yet, forthcoming. Most polymer chemists will find this a rather amenable point of view, and it is to be hoped that many will turn their attention to devising experiments which will show that there is some reason for a triplet corresponding to a particular amino acid and not to some other one. This remains to be proved in the laboratory and is still a subject of considerable controversy.

Let us now return to the possible ways in which the proteins and nucleic acids might have come into being in a nonliving world: The world with which we are dealing is a world in water; it is not a world in methylene chloride, dioxane, DMF, or other solvents. And all of the reactions which are described in Figure 1 occur in water. Whatever reactions we use, whatever reactions we call upon to do the originating of the protein and the nucleic acid, should be essentially in an aqueous medium to begin with. This can be modified somewhat by the resulting polymer itself in terms of the protein-lipid interaction. The reactions do, however, occur primarily in an aqueous environment.

We set out to try and generate polypeptides and other polymers in an aqueous environment[2]. Chemically and thermodynamically this is rather a difficult operation. The formation of the biopolymer from the monomer is, in the case of the proteins, nucleic acids, carbohydrates, and lipids, the result of a dehydration condensation. To make a dehydration condensation occur in water is a tricky operation. Living organisms have long ago learned how to do this, but the

question now is whether we, as chemists, can accomplish something similar. The reactions which must be accomplished in this aqueous environment are shown in Figure 2. The

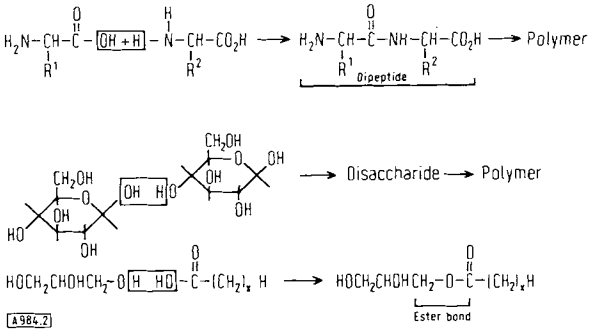


Fig. 2. Dehydration condensation in the formation of polypeptides, carbohydrates, fats.

proteins and peptides are formed from a bifunctional molecule, from which a water molecule can be eliminated, a bifunctional dimer remaining which, in turn, can grow at either end. Formally, the same kind of system occurs in each of the four cases—proteins, polysaccharides, lipids, nucleic acids. In each case, the water molecule is eliminated and a new bifunctional molecule is formed. This type of operation can go on continuously, but, in the case of the lipids, not to the same extent as with the proteins or polysaccharides; elimination of water gives rise to the ester bond which can react further. This is, however, not quite in the same category but it is possible to make fairly large molecules. This case has been mentioned at this point, since the lipids play an important role in the whole evolutionary scheme.

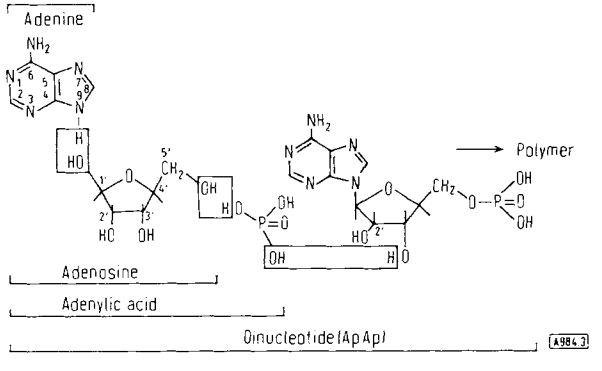


Fig. 3. Dehydration condensation in the formation of polynucleotides.

Figure 3 shows the methods for the formation of the nucleic acids by dehydration condensation reactions. Here, actually, there are three points of dehydration involved. The first cleavage of water effects formation of the amino glycoside on a base, whereby the NH group of the base reacts with the glycosidic semiacetal hydroxy of the sugar. The second takes place between the phosphate ester and the primary hydroxy group with formation of the terminal 5′-phosphate. In this case the ribose sugar is shown which forms RNA. (The DNA, of course, is the material in which the 2′-carbon lacks the hydroxyl, *i. e.*, carries two hydrogen atoms). The third dehydration condensation occurs between the monophosphate ester and the secondary hydroxy group on the 3′-carbon atom of another nucleotide. The result is a bifunctional molecule, with both functions available; at one end the phosphate ester is available and at the other end the 3′-alcohol hydroxy group. The nucleic acids are built on the same principles as the two other major biopolymers shown in Figure 2.

We asked the question: Is there any way to generate the polypeptides? Many reactions are known which might be used for the linking of polypeptide bonds in an aqueous environment. Only a slight modification of the existing knowledge of reactions was required. One of the important reagents that has been used for the dehydration condensation of a variety of functional groups is the carbodiimide R—N=C=N—R[*]. The carbodiimide structure has the ability to remove water, in stages, by more or less specific reactions with acid groups such as carboxyl, phosphate, and certain alcohols. This leads to condensation reactions[3]. Carbodiimide has been used widely for nucleotide and polypeptide synthesis, but usually not in aqueous environments. It was necessary to change the R groups, to make them useful in aqueous environments. This can be achieved by making the R groups hydrophilic so that the carbodiimide can be dissolved in water. This is useful since the carbodiimide does not hydrolyze very rapidly directly but does so by virtue of its reaction with the carboxyl group and then with the phosphate.

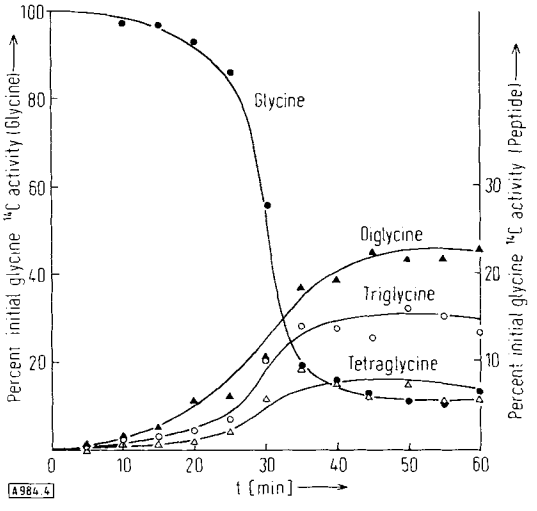


Fig. 4. Polypeptide formation by dicyandiamide in homogeneous solution.

Now arose the next question: How could this type of reaction occur in a natural environment? It turned out that there was a very easy way in which this particular structure could have evolved in a natural environment. As we know, ammonia and HCN were two of the primary molecules on the earth's surface. Reactions between these two materials can lead to cyanamide, probably through cyanic acid or hydroxylamine. Cyanamide is a tautomeric form of carbodiimide which, however, is not stable; it tends to dimerize to the dicyandiamide (DCDA) $H_2N—C(=NH)—NH—CN$, which is the common form of cyanamide. It also contains the same type of π-bonds as carbodiimide. We used DCDA as one of the starting materials to demonstrate this type of dehydration condensation in the formation of biopolymeric materials. We took an amino acid, adjusted the pH to slightly acid conditions, and added the water-soluble carbodiimide material (dicyandiamide) to

[*] R = *e. g.* cyclohexyl.

see if we could produce polypeptides in the homogeneous aqueous environment. The results of some of these experiments are shown in Figure 4[4]. We started with glycine and carried out the reaction at pH 3.5; the glycine disappears and the dimer (diglycine), trimer (triglycine), and tetramer (tetraglycine) are formed. The reaction is very slow and does not proceed very far. One can hardly call the tetraglycine a "polymer", but at least the reaction does occur in aqueous solution.

The next question was: Is the reaction in any way selective? Do the amino acids self-select each other when they condense? This is a natural question to ask in the ordinary course of evolutionary studies. About five or six years ago, *Steinman*, in trying to answer this question, attached an amino acid B on polymer beads *via* the carboxyl group and used an amino protected amino acid A to couple to it. He measured the relative rates of coupling of amino acid A to the polymer-bound amino acid B in an homogeneous environment; this is a model, of sorts, for polypeptide formation. Table 1 shows the relative rates of coupling. It can be seen that the rates differ by a factor of about ten[5]. The is the measured coupling efficiency, and the calculation is based upon the frequency of a particular pair (phenylalanylglycine, glycylphenylalanine, or isoleucylglycine, *etc.*) in today's existing proteins with a statistical analysis of the situation, normalizing the frequencies to glycylglycine as unity. There seems to be slight relationship between the efficiency of coupling in the heterogeneous system and the occurrence in nature of these particular pairs of peptides. This idea has been developed still further, and there are now better ways of studying the possible self-selection of amino acids in peptide formation.

Table 1. Comparison of experimentally determined dipeptide yields and frequencies calculated from known protein sequences relative to Gly-Gly = 1.0.

Dipeptide [a]	Values Obs.	Calc.
Gly-Gly	1.0	1.0
Gly-Ala	0.8	0.7
Ala-Gly	0.8	0.6
Ala-Ala	0.7	0.6
Gly-Val	0.5	0.2
Val-Gly	0.5	0.3
Gly-Leu	0.5	0.3
Leu-Gly	0.5	0.2
Gly-Ile	0.3	0.1
Ile-Gly	0.3	0.1
Gly-Phe	0.1	0.1
Phe-Gly	0.1	0.1

[a] The dipeptides are listed in terms of increasing volume of the side chains of the constituent residues. Gly = glycine, Ala = alanine, Val = valine, Leu = leucine, Ile = isoleucine, Phe = Phenylalanine. Example: Gly-Ala = glycylalanine [5].

There are two other methods by which polypeptides have been made, one of which was carried out in a nonaqueous environment. Table 2 shows the results of experiments in which *Sidney Fox* used molten glutamic acid containing a small amount of pyrophosphoric acid as a solvent (hardly an aqueous environment) and to which an equimolar mixture of all the other amino acids, other than aspartic and glutamic[6], was added. Here, again, it can be seen that the incorporation into the resulting polypeptides is not statistical. The main point about these data is that they show the variable frequency of incorporation, ranging from 0.5% to 5%, and that selectivity is evident.

The final study is, perhaps, the most elegant, and one doesn't know whether it will continue. This is the work of *Aharon Katchalsky*, who used aminoacyl adenylates as starting material and montmorillonite clay as the catalyst, both of which are readily available in nature. The aminoacyl adenylate is available in nature because the adenylic acid can be generated by ordinary chemical reactions and the coupling of the amino acid to the adenylic acid (linking a phosphate and a carboxyl anhydride) can be easily achieved using the carbodiimide dehydration condensation reaction in an aqueous environment. So the system with which *Katchalsky* began is achievable biologically. *Katchalsky*'s discovery ought to be described in detail because it is the starting point of a very interesting idea. The aminoacyl adenylate used is the activated amino acid in the first stage of normal biological amino acid activation; although it is usually a part of an enzyme complex it, nevertheless, is a suitable starting material for this type of study. At first, *Katchalsky* tried to polymerize this material in a homogeneous aqueous solution. The aminoacyl adenylate can be regarded as a mixed anhydride of a carboxylic acid group and phosphoric acid which also contains the free amino group of the amino acid. Thus, the free amino group can act as a nucleophile toward the carboxy group of the anhydride grouping.

Table 2. Amino acid composition of proteinoid prepared in the presence of 200 ppm of pyrophosphoric acid. Asp: Glu: equimolar mixture of basic and neutral amino acid = 2:1:3, *i.e.*, 33%:16%:50%. The mixture was incubated for 150 h at 100 °C.

Amino acid	%	Amino acid	%
Thr	0.55	Lys	2.79
Ser	0.63	His	2.53
Gly	2.93	Arg	1.83
Ala	1.31	Total	7.15
Val	1.33		
Met	0.86	Asp	51.9
Ile	0.71	Glu	13.3
Leu	3.44	Total	65.2
Tyr	3.87		
Phe	5.87		
NH_2	5.02		
Total	27.6		

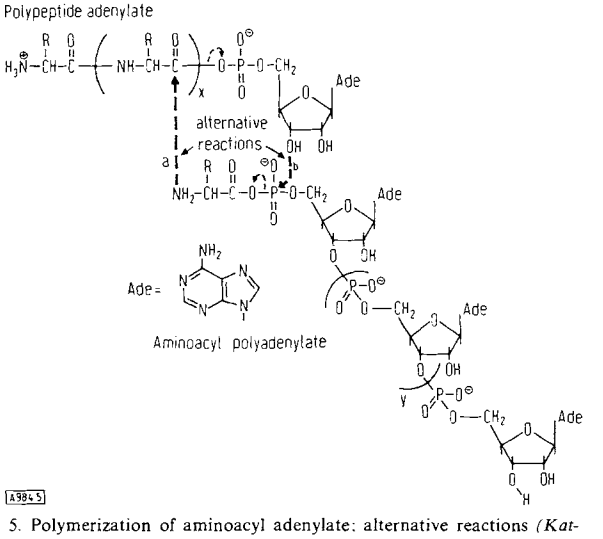


Fig. 5. Polymerization of aminoacyl adenylate: alternative reactions *(Katchalsky)*.

Figure 5 outlines *Katchalsky*'s basic idea; but it shows more as well. If one considers the aminoacyl adenylate skeleton attached to the polynucleotide chain one can see that the amino group can act as a nucleophile toward the acyl group of the anhydride (reaction a), a reaction that leads to the formation of a polypeptide (poly)adenylate and free adenylic acid. The alternative reaction, which *Katchalsky* had considered, but had not published any experimental information on, is that in which the secondary hydroxy of the sugar will attack—once again as a nucleophile—the phosphate in the mixed anhydride (reaction b), resulting in the reverse type of polymerization, the products being a free amino acid and the (poly)aminoacyl polyadenylate. There are, of course, alternative reactions which can occur (rearrangements, *etc.*) to stop or slow down the polymerization reactions.

As *Katchalsky* reported in his publication of 1970[7a] and in more detail in May 1972[7b] in Göttingen, shortly before his death, the reaction is slow in homogeneous solution and the polymers which are formed are not very large (8—10 units). He found, however, that if he performed this reaction in the presence of a properly prepared montmorillonite, the whole system changed. The reaction became extremely rapid and the polypeptides reached fairly high degrees of polymerization—*i.e.* high for this kind of a reaction[8].

We have both attempted this type of reaction and have, indeed, been able to prepare polypeptides and polynucleotides from the same starting material. We can now begin to see the real relationship between the polynucleotides and polypeptides—or the nucleic acids and proteins—and how they can arise as a result of the stereochemistry of the reaction.

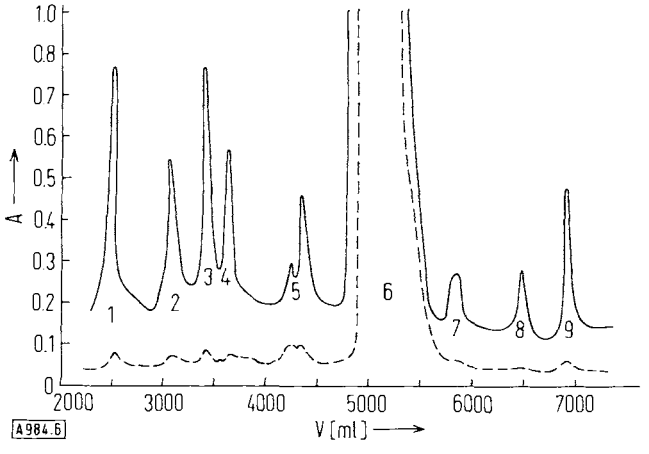


Fig. 6. Polypeptides from alanyl adenylate on montmorillonite *(Katchalsky)*. Chromatography of fraction II on Sephadex G-25 with gel bed 3 × 4 × 150 cm. 1—9, see text and Table 3.

Katchalsky found that a number of discrete polypeptides were formed from alanyladenylate and montmorillonite. Figure 6 shows a chromatogram of the second fraction. Table 3 gives more information about the two principal components contained in the initial extract of this reaction. Fraction I consists mostly of adenylic acid and three types of polypeptides. Fraction II, however, contains mostly polypeptides with some adenylic acid. In the gel permeation chromatogram of fraction II (Figure 6) one can see the presence of some nine components; the largest component is adenylic acid, and the components 1, 2, 3 and 4 are polypeptides. In addition, there are two

Table 3. Composition of the main fraction obtained from 1 g alanyl adenylate on montmorillonite.

Fraction	Component	MW	Degree of polymerization	Wt. [mg]	No. in Fig. 6
I	Peptide	640	9	10.3	
	Peptide	1120	16	35.2	
	Peptide	1900	27	20.0	
	Adenylic acid		1	470.5	
II	Peptide adenylate	2130	30	8	4
	Peptide adenylate	2310	32	5.2	2
	Peptide adenylate	3020	42	10.8	1
	Peptide adenylate	4000	56	17.1	3
	Adenylic acid		1	260.1	6

unidentified inorganic salts and two unidentified organic compounds. When I spoke to *Katchalsky* he said he thought they might be polynucleotides; and I think so too.

Perhaps someone else will pursue this work further in the future: In my opinion it represents an extremely important step towards understanding the nature of polymerization reactions. Why is it that you do not get a random distribution but discrete groups of polymers? I think these discrete groups occur because no simple addition reaction takes place. Amino acids are added and polynucleotides are constructed and subsequently form a polypeptide-polyadenylate, and these materials regulate the size of the polypeptides which are found. It will probably turn out that the polynucleotide is also discrete in some way.

3. The Origin of the Genetic Code

It is known that in today's living organisms the specification of the linear array of amino acids in a polypeptide is contained in a corresponding linear array of bases in a polynucleotide. A series of three bases in the polynucleotide (DNA) specifies a specific amino acid in a polypeptide, or protein. This correspondence of a triplet of bases with a particular amino acid is universal in all living organisms. One form of expressing

Table 4. The genetic code.

second letter	first letter: A		C		G		U	
A	AAA	Lys	CAA	Gln	GAA	Glu	UAA	termi-
	AAG		CAG		GAG		UAG	nate
	AAC	Asn	CAC	His	GAC	Asp	UAC	Tyr
	AAU		CAU		GAU		UAU	
C	ACA	Thr	CCA	Pro	GCA	Ala	UCA	Ser
	ACG		CCG		GCG		UCG	
	ACC		CCC		GCC		UCC	
	ACU		CCU		GCU		UCU	
G	AGA	Arg	CGA	Arg	GGA	Gly	UGA	termi-
	AGG		CGG		GGG		UGG	nate Trp
	AGC	Ser	CGC		GGC		UGC	Cys
	AGU		CGU		GGU		UGU	
U	AUA	Ile	CUA	Leu	GUA	Val	UUA	Leu
	AUG	Met	CUG		GUG		UUG	
	AUC	Ile	CUC		GUC		UUC	Phe
	AUU		CUU		GUU		UUU	

this is shown in Table 4. Here one can see there is a certain amount of redundancy in the code, but the universality of it throughout the living world is now fairly well established.

Thus, in addition to the question of how these biopolymers may actually have been formed abiogenically we must turn to the question of how the linear relationship between the two major biopolymers, that is, the polypeptides (proteins) and the polynucleotides (DNA), evolved. That is: What is the possible origin of the genetic code?

There are those who believe that the particular specificity we now find in living organisms between a particular triplet and a particular amino acid, as assembled in Table 4, is the result of an accident in some early catalytic reaction which, by virtue of a selective advantage in producing autocatalytic systems, has now been frozen into *all* of biology[9]. Selection followed because a single autocatalytic system eventually dominated all the others. Another way of expressing this "frozen accident" notion is to state that a renewed chemical evolution under exactly the same starting conditions could very well lead to a completely different codeal relationship[10, 11]. It is my personal belief, however, that this would *not* be the case. I believe that the codal relationship reflects some characteristic molecular interactions between amino acids (polypeptides) and nucleotides (polynucleotides).

A modicum of evidence for this already exists in the form of some experiments carried out on the rate of coupling of amino acids to nucleotides. Some years ago[12] we attached a nucleotide (adenylic acid) to a synthetic polymer (polystyrene); the polystyrene was in the form of microspheres. The next step was to measure the rate of coupling of two different amino acids to each of these two polystyrene-nucleotide preparations. The coupling was performed using an *N*-protected amino acid adenylate. The reaction is shown in Figure 7

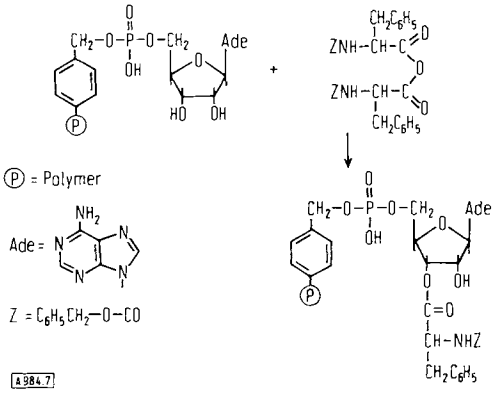


Fig. 7. The coupling of a polymer-AMP complex with the anhydride of an *N*-protected amino acid (24h at room temperature in pyridine) to an *N*-protected phenylalanyl-AMP polymer.

and the results, as well as those of analogous reactions, are given in Table 5[13]. It can be seen that glycine reacts more rapidly with adenine and cytosine than does phenylalanine, and adenine reacts more rapidly with both amino acids than does cytosine. The overall range of reactivity is roughly a factor of three.

Here the beginning of a kind of selectivity in a reaction rate is apparent[14]. However, I believe that this kind of selectivity will be very much enhanced if both the amino acid and the nucleotides are each, respectively, part of a polymer. For example, one would expect the alternative reactions (a) and (b) indicated in Figure 6 to be very dependent upon the nature of the amino acid and the nature of the nucleotide

Table 5. Coupling of a polymer-nucleotide complex with the anhydride of an *N*-protected amino acid. The proportion [%] of bound nucleotides reacted are quoted.

Amino acid \ Base	Adenine	Cytosine
Phenylalanine	6.7	2.9
Glycine	10.0	6.5

involved. Furthermore, one would expect that selectivity would be increased with the length and character of the polynucleotide, on the one hand, and possibly even with the polypeptide on the other. This last experiment is yet to be done, but is underway.

4. Secondary and Tertiary Structure of Protein and Interaction with Nucleic Acids

This part of our discussion will be concerned with what is known about the secondary, tertiary and quaternary structures, above all, of proteins. There are several principles which should be emphasized here: One is the way in which proteins fold up, in their secondary and tertiary structures, another is the way enzymes interact with substrates, and a third is the way in which the proteins interact with the nucleic acids. (The protein-lipid interaction is discussed in Section 5.)

Myoglobin, with its tertiary structure, is shown in Figure 8. The left-hand side of the figure shows the alpha helical structure and the drawing on the right-hand gives a more three-dimensional view of the same material, to show that the myoglobin is a folded protein, with the heme stuck in the center. This secondary and tertiary structure is built into the molecule as a result of the amino acid sequence in the polypeptide which takes up this structure, given the opportunity, in water[15]. In the structure of cytochrome c, the hydrophobic sidechains of the amino acids are more or less in the middle of the molecule and the hydrophilic parts are on the outside of the molecule. This is the only characteristic which has so far approached a generalization on the structure of soluble proteins. In general, the structure of soluble proteins is such that when they fold up in their secondary and tertiary structures they do so in a way which places the hydrophobic chains on the inside (away from the water environment) and the hydrophilic chains on the outside, towards the water environment.

It is for this reason that I had the reservation, mentioned earlier, about the generation of polypeptide and polynucleotide structures in a purely aqueous environment. Modifications can occur during the course of formation of these biopolymers which will remove their functions from the water environment into a nonaqueous environment, by virtue of their own structure, so to speak.

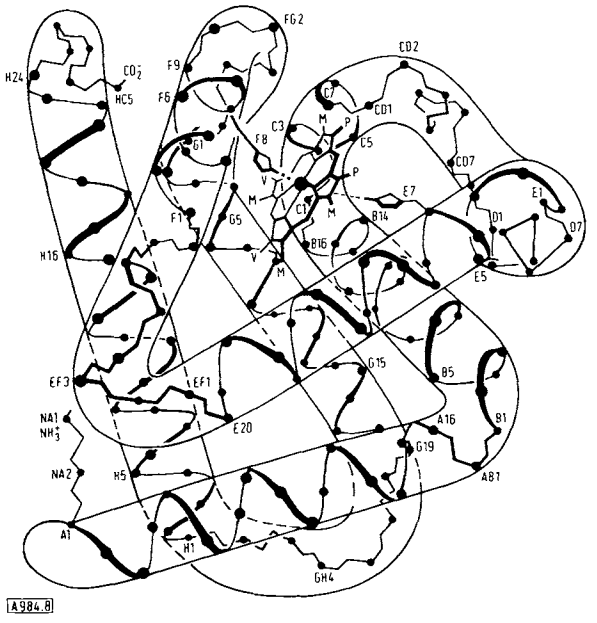
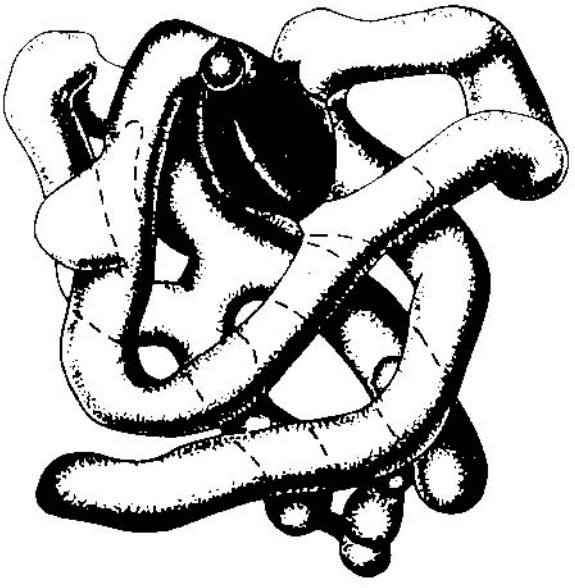


Fig. 8. Tertiary structure of myoglobin.



The lysozyme molecule has a cleft, into which the substrate is incorporated. Figure 9 shows the mechanism of the polysaccharide hydrolysis, and the actual function of the active site.

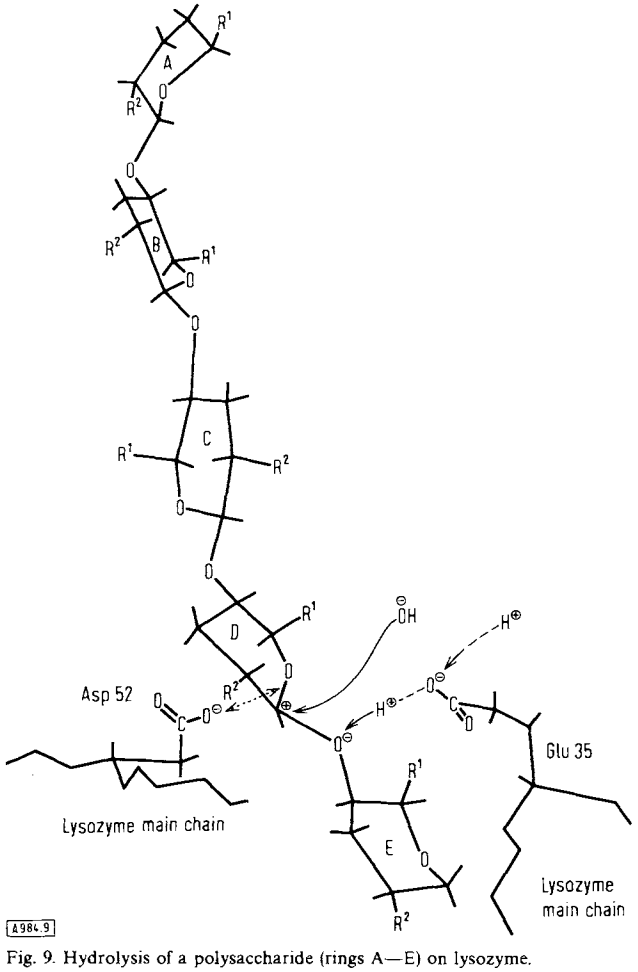


Fig. 9. Hydrolysis of a polysaccharide (rings A—E) on lysozyme.

One can see how the polysaccharide lies in the active site of the lysozyme. The glycosidic linkage is hydrolyzed: one part of the substrate is transferred to the polymer (Asp 52) thus letting the other part go free. The Asp glycosidic ester, in turn, is very rapidly hydrolyzed. This is the way in which the hydrolytic enzymes and many of the transferases function. Thus, the tertiary structure is evolved to give the particular tertiary architecture which will take hold of the proper substrate.

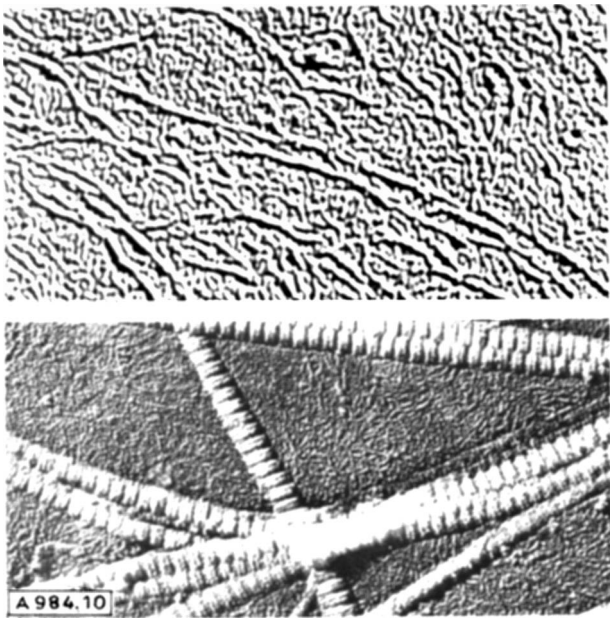


Fig. 10. Structure of collagen. For details see text.

The next figure (which is an old one) reaches into the area visible under the electron microscope. In collagen (Fig. 10), we can see that molecules can be refolded into their tertiary structure and, even further, that these molecules can actually reassemble into more complex quaternary structures which are dependent upon their primary sequence[16]. The upper part of Figure 10 shows the separated collagen fibrils, and the bottom part the reaggregated fibrils, which strongly resemble the natural ones. The fibrils are highly ordered arrays as a result of protein-protein aggregation.

The next few figures show the dissociation and re-aggregation of the tobacco mosaic virus (a relatively simple virus particle) which consists of a set of identical protein molecules and

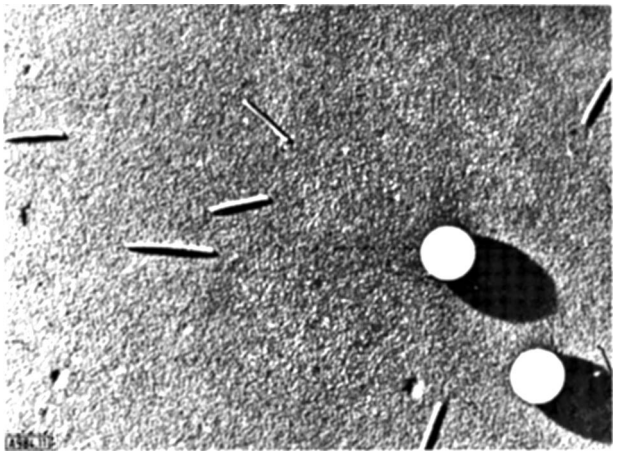


Fig. 11. Tobacco mosaic virus (TMV), native.

one nucleic acid molecule. These two can be separated and then reassembled again into a complete virus particle[17]. More

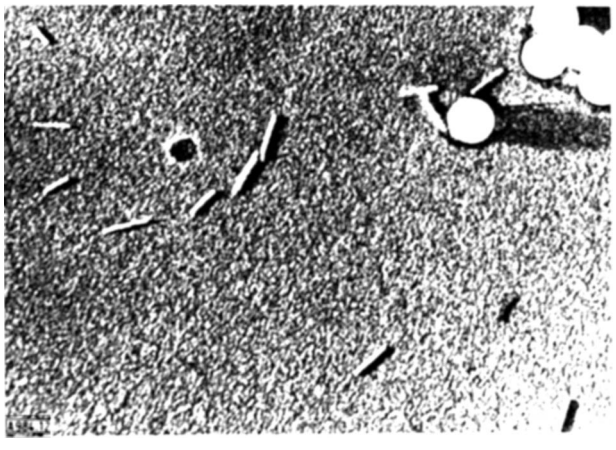


Fig. 12. Reconstituted TMV protein.

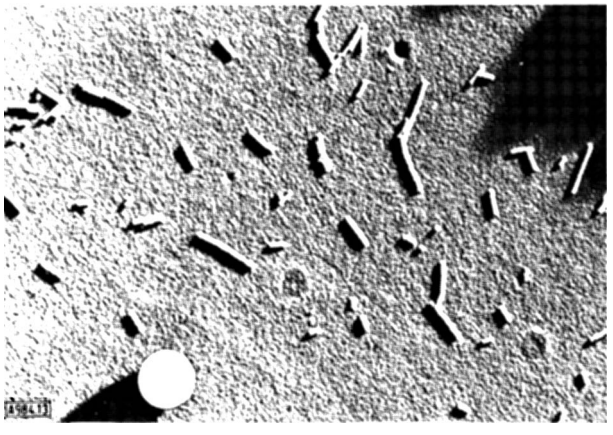


Fig. 13. Reconstituted TMV.

complex virus particles have now been reconstituted as well. Figure 11 shows the native tobacco mosaic virus (TMV), with its uniform particles, and Figure 12 shows the reassembly of the TMV protein without the nucleic acid. The protein is separated from the nucleic acid, redissolved, and, by changing the salt concentration, reaggregated with the result shown here. One can see that the material has reaggregated with the correct dimensions in one way, but not in the other; in contrast to the native TMV, all the particles have different lengths because there is no nucleic acid "information" to give the correct dimensions. In Figure 13 you can see the reconstituted TMV virus particle, which occurs when the nucleic acid component is put back into the protein solution. This same type of experiment has been done with much more complex particles such as T4 bacteriophages, MS2 phages, *etc.* Progress is also being made in the reassembly of very complex structures[18]. The TMV particle itself is shown diagramatically in Figure 14. The tertiary structure of the subunit protein material in TMV has not yet been established, but we know that there is a sequence of 120 amino acids.

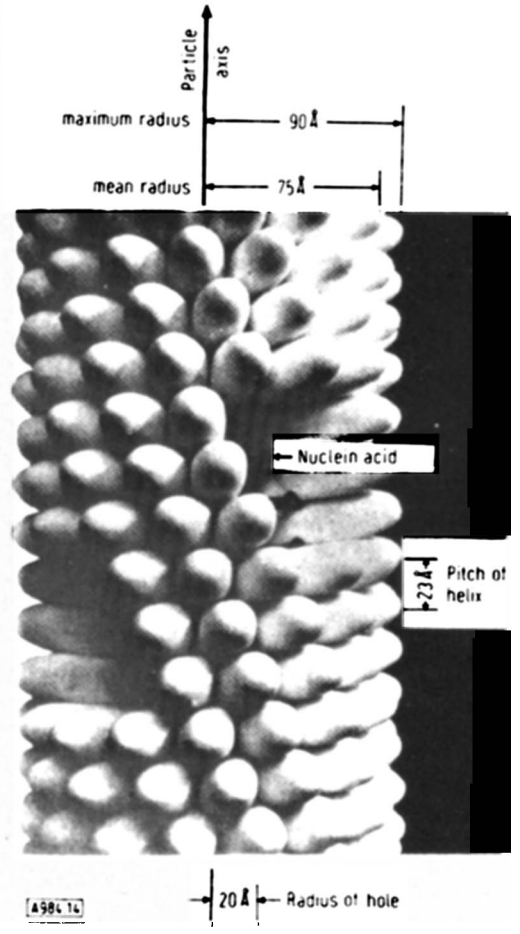


Fig. 14. Diagrammatic structure of TMV.

5. Interaction of Protein and Lipids

Protein-lipid interaction is one of the areas of very high scientific activity, in the technological polymer area and more selectively than hithertofore in the biochemical laboratory. Lipids have been used for handling biochemical proteins for some time. The present concept of membrane structure—protein embedded in the bilipid membrane—is shown in Figure 15. A phospholipid consists of the hydrophilic ends (the phos-

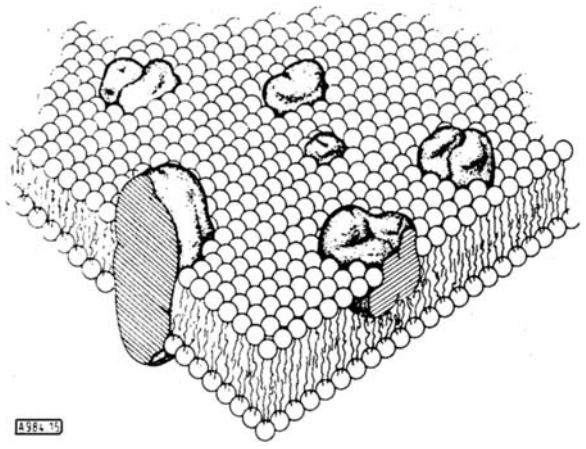


Fig. 15. Present concept of membrane structure showing protein embedded in bilipid membrane.

phoethanolamine end represented by spheres) and the lipid chains. The globules which are membrane proteins in various stages of insertion into the bilipid membrane make the total actual biological membrane itself. These proteins may be either structural elements or transport proteins, which carry material into the cell through the biological membrane. The fact that many of the proteins are directly associated with lipids implies that there must be hydrophobic connections on the outside of the proteins in order to be able to perform this type of insertion. This has not yet been established in the laboratory. Clearly, there are hydrophobic parts on the proteins, but whether they are on the outside or the inside, or both, is a subject of some concern.



Fig. 16. Liposomes of phospholipid and cytochrome *(Horne* and *Watkins)*.

A synthetic "biological cell" is shown in Figure 16. These liposomes (soft spheres) are formed by shaking the solution of a phospholipid (lecithin) with a protein cytochrome. The multiple and single bilipid layers are visible in the electron micrograph; these layers are filled with protein[19]. This work was done about eight years ago in Great Britain. I have called the spheres "Bangasomes" after the man who first constructed them[20]. The spheres are generally called liposomes; their osmotic properties, transport properties, and a variety of other properties resemble those of living cells. How do materials get in and out through that membrane? What is the mode of their transport? Can specific proteins be associated with the membranes to produce these specific results? These are questions still unanswered. Studies are now in progress; this field is really just blossoming out as a new area and marks the advent of a new era. Only now have the polymer physical chemists become active in this field.

As is known, it is quite common to use detergents, anionic, cationic and non-ionic, for the isolation of a particular enzyme from a living cell. The procedures for the soluble proteins (soluble enzymes) are now well established. The insoluble enzymes, however, are a different story. The isolation of membrane-attached enzymes from the membrane of the cell, the membrane of the mitochondrion, or the membrane of other internal cellular structures present more difficulties; it is necessary to use detergents of various types for enzyme extraction. A few years ago, we naively (and this quality has some merits as well as demerits) began to isolate the enzymes in which we were interested (the RNA-instructed DNA polymerase, RIDP). We had to learn that detergents are necessary. We also learned that when the detergents were eliminated, the enzyme itself seemed to be eliminated, or at least the activity of the enzyme was eliminated. This gave rise to the idea that perhaps the activity of the enzyme was dependent upon the presence of detergent molecules, *i. e.*, the lipid component in some way was changing the conformation of the enzyme and inducing its activity, or at least raising it. Therefore, the residual enzyme activities which are observed when synthetic detergents are *not* used for extraction are simply due to the natural phospholipid, which was released when the solution was sonicated.

We found that when we added small amounts of certain types of non-ionic detergents it was possible to recover the enzyme activity. This constitutes a new development. No one really believed that the intrinsic activity of the enzyme was dependent upon its association with a detergent molecule. Previously it has been assumed that the detergent molecules are solubilizing entities to dissolve the enzyme out of the lipid membrane. The detergent does, in fact, take the enzyme out of the lipid membrane, but large amounts of the detergent are not needed to make the enzyme active.

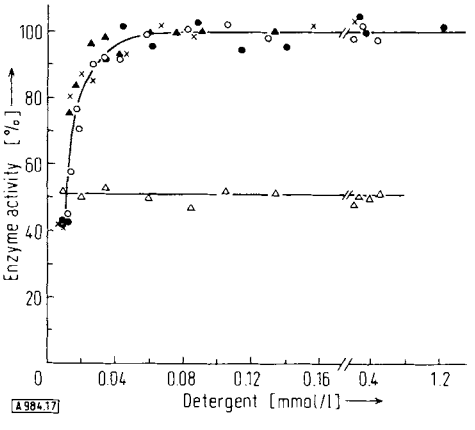


Fig. 17. Activation of RNA-instructed DNA polymerase by detergent. 100% = maximum activity.

The activation of the RNA-instructed DNA-polymerase by detergents is shown in Figure 17. RIDP is the enzyme which copies RNA into DNA, which is popularly known as "reverse transcriptase activity". Research on this enzyme resulted in one of the major breakthroughs of the last two or three years in this field, particularly in connection with tumor viruses. The activity of the enzyme is increased by addition of suitable amounts of various types of non-ionic detergents[21, 22]. On a molecular basis, this is a positive molecular interaction. Observation of interaction happened to be made during the development of techniques for the study of enzymes. Not uncommon to this type of work, this turned out to be the central problem.

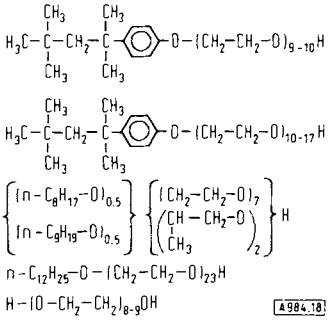


Fig. 18. Structure of detergents used in RNA-instructed DNA polymerase activation. From top to bottom: Triton X-100, Triton X-1017, Triton DN 65, Brij 35, polyethylene glycol-400.

We were actually studying the inhibition of the RIDP enzyme activity by certain drugs with a view toward the possible use of such drugs to inhibit the transformation of normal cells into cancer cells by the viruses which carry this enzyme. The RIDP enzyme copies the virus-RNA in DNA which is then inserted into the DNA of the cell, thus making a transformed cell. The rationale was to find a drug which would inhibit the RIDP enzyme and thus block the transformation into cancer cells. This meant that we had to study inhibition of the enzyme activity under various conditions. It also gave rise to our studies on the effect of detergents on enzyme activity. We found that we had some excellent enzyme inhibitors in the drug itself. Rifampicin and its derivatives are lipophilic substances. Here, it turns out that if there is too much

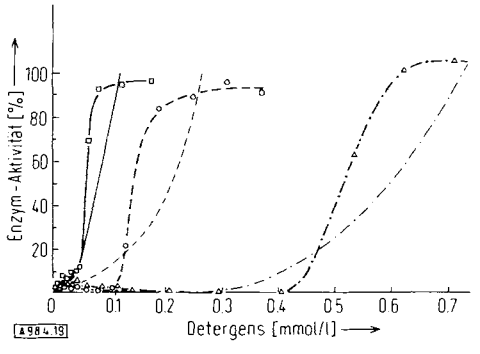


Fig. 19. Suppression of drug effect on RNA-instructed DNA polymerase by detergents (□, ○, △) (see text).

detergent the drug is ineffective in its inhibition of RIDP enzyme activity.

The structure of the non-ionic detergents which were used in this study is shown in Figure 18. Some of the detergents (the Tritons) are aromatic and others are not. This fact is important. The effect of three different detergents on the ability of a certain drug, which has a hydrophobic tail and a hydrophilic end, to inhibit the enzyme is shown in Figure 19. An attempt was made to plot the critical micelle concentration for each of the detergents. The ability to deter the drug from inhibiting the enzyme is dependent upon micelle formation[22]. We interpret this finding as follows: if there is too much detergent present there is micelle formation; the micelles dissolve the drug, and thus remove it from the hydrophobic portion of the enzyme. The drug no longer can act on the enzyme, so the enzyme returns to its full activity.

Figure 20 shows two magnifications of a tissue culture which has been transformed into malignancy. As soon as the cells have been transformed into malignancy they overgrow each other, and they make little "piles" called foci. We have found that by suitable adjustment of the drug concentration it is possible to prevent the virus from transforming cells as determined by this focus formation inhibition[23]. We have even gone a stage further and been able to show that the formation

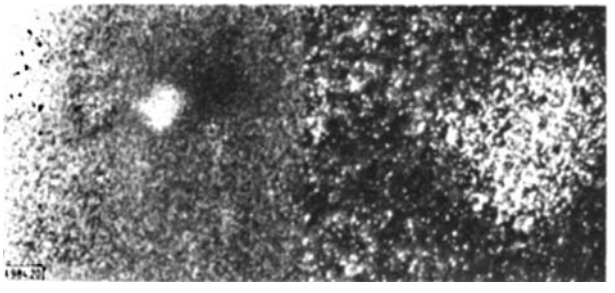


Fig. 20. MSV focus formation on Balb/3T3 cells (dark field illumination).

of tumors in whole animals can be prevented[24]. Again, this required a suitable combination of detergent and drug to prevent the detergent from spoiling the activity of the drug.

I hope that some of the things described above will give the reader some concept of the kind of a china shop one can get into, if one has the will to do it. I have tried to give those of you who are not in the biochemistry-molecular biology business some idea of the way in which a polymer chemist could influence the development of our fundamental concepts of the nature of life, its origin, and the application of our knowledge to the problems of the day.

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[1] *P. J. Flory*, Angew. Chem. *86*, 109 (1974); Angew. Chem. internat. Edit. *13*, 97 (1974).

[2] *M. Calvin*: Chemical Evolution. Oxford University Press, Oxford, England 1969, p. 152ff.

[3] See Ref. [2], p. 161ff.; *D. H. Kenyon* and *G. Steinman*: Biochemical Predestination. McGraw-Hill, New York 1969, p. 182ff.

[4] *D. H. Kenyon, G. Steinman*, and *M. Calvin*, Biochim. Biophys. Acta *124*, 339 (1966).

[5] *G. Steinman* and *M. N. Cole*, Proc. Nat. Acad. Sci. USA *58*, 735 (1967).

[6] *K. Harada* and *S. W. Fox* in *S. W. Fox*: Origins of Prebiological Systems and Their Molecular Matrices. Academic Press, New York 1965, p. 296.

[7] a) *M. Paecht-Horowitz, J. D. Breger*, and *A. Katchalsky*, Nature *228*, 636 (1970); b) *M. Paecht-Horowitz*, Angew. Chem. *85*, 422 (1973); Angew. Chem. internat. Edit. *12*, 349 (1973).

[8] *M. Paecht-Horowitz* and *A. Katchalsky*, J. Mol. Evol. *2*, 91 (1973).

[9] *M. Eigen*, Naturwissenschaften *58*, 465 (1971); cf. *H. Kuhn*, Angew. Chem. *84*, 838 (1972); Angew. Chem. internat. Edit. *11*, 798 (1972).

[10] *F. H. C. Crick*, J. Mol. Biol. *38*, 267 (1968).

[11] *L. E. Orgel*, J. Mol. Biol. *38*, 381 (1968).

[12] *M. A. Harpold* and *M. Calvin*, Nature *219*, 486 (1968).

[13] *M. A. Harpold* and *M. Calvin*, Biochim. Biophys. Acta *308*, 117 (1973).

[14] *M. Calvin*, Proc. Roy. Soc. Edinburgh, Section *70*, 273 (1969).

[15] For a discussion of the principles involved in three-dimensional structure and self-assembly, see Ref. [2], pp. 187—193.

[16] For a discussion of the principles involved in quaternary structure, see Ref. [2], p. 196.

[17] For a discussion of reassembly, see Ref. [2], pp. 216—218.

[18] *D. J. Kushner*, Bacteriol. Rev. *33*, 302 (1969).

[19] *D. Papahadjopoulos* and *N. Miller*, Biochim. Biophys. Acta *135*, 624 (1967); *D. Papahadjopoulos* and *W. Watkins*, *ibid.* *135*, 639 (1967).

[20] *A. D. Bangham, J. DeGier*, and *G. D. Greville*, Chem. Phys. Lipids *1*, 225 (1967).

[21] *F. M. Thompson, L. J. Libertini, U. R. Joss*, and *M. Calvin*, Science *178*, 505 (1972).

[22] *F. M. Thompson, L. J. Libertini, U. R. Joss*, and *M. Calvin*, to be published.

[23] *M. Calvin*, Radiation Res. *50*, 105 (1972).

[24] *U. R. Joss, A. M. Hughes*, and *M. Calvin*, Nature, New Biol. *242*, 88 (1973).

COMMUNICATIONS

cis-trans-Isomerism of Thyrotropin Releasing Hormone (TRH) in Aqueous Solution[**]

By *Wolfgang Voelter, Oskar Oster*, and *Karl Zech*[*]

A prerequisite for explaining the mode of action of peptide hormones is an accurate knowledge of their structure. Since nuclear magnetic resonance measurements can yield a wealth of information about the structure of dissolved peptide molecules we have investigated synthetic[1] TRH by pulse Fourier transform ^{13}C-NMR spectroscopy[2][***].

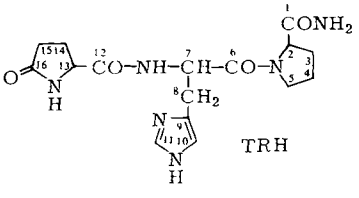


Figure 1 shows the broad-band proton decoupled spectrum of TRH. Almost all the signals can be assigned by comparison with the spectra of simple amino acids, TRH derivatives, and derivatives of TRH components obtained as intermediates in the synthesis of the hormone. An additional aid for assignment of the signals is provided by the proton off-resonance spectrum[1].

Remarkably, as can be seen in Figure 1, the intense signals of the C-atoms 3, 4, 5, and 6 are each accompanied within a distance of 1—2 ppm by a further signal (3', 4', 5', and 6', resp.) whose intensity is only 10—20% of the remaining signals.

To explain this phenomenon we have synthesized the proline derivatives and proline-containing dipeptides and recorded their ^{13}C-NMR spectra.

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[**] This work was supported by the Deutsche Forschungsgemeinschaft.

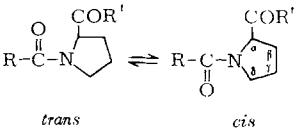
[***] All the compounds investigated have rotations, melting points, and analytical data as given in the literature; for the preparation of the substances cf. Refs. [1, 5]. The PFT ^{13}C-NMR spectra were recorded on a Bruker HFX-90 multinuclear NMR spectrometer (22.628 MHz for ^{2}H; pulse width 4—5 μs; pulse interval 0.41 s).

The carbon atoms of the proline ring of Boc-Pro-NH_2 give rise to two signals (Fig. 2). The spectrum can be interpreted only in terms of the presence of a *cis-trans* isomeric pair. ^{13}C-NMR spectroscopy thus proves to be an excellent tool for the detection of *cis*- and *trans*-isomers of proline compounds; previously, these were mainly differentiated by proton resonance spectroscopy[3].

Although the intensities of PFT ^{13}C-NMR resonances are not suitable for quantitative determinations they can provide a rough estimation of the equilibria of chemically similar carbon atoms. Thus, a comparison of the intensities of the ^{13}C-NMR signals of proline carbon atoms would indicate that 20—30% of the *cis* and 80—70% of the *trans* isomers of Boc-Pro-NH_2 are present in equilibrium in aqueous solution at room temperature.

The assignment of signals to the *cis* or *trans* isomers by ^{13}C-NMR spectroscopy is also possible in the case of Boc-Gly-Pro. ^{1}H-NMR investigations[3] have already shown that solutions of this compound contain up to 70—80% of the *trans* isomer. The more intense resonances of the proline carbon atoms in the PFT ^{13}C-NMR spectrum of Boc-Gly-Pro can therefore be assigned to the *trans* isomer.

Furthermore, the positions of the proline carbon-atom signals in the spectrum of glycylproline are characteristic for the *cis* isomers of prolines.



On the basis of these findings the resonances of the C^{α}, C^{β}, C^{γ}, and C^{δ} atoms of the proline rings of the compounds listed in Figure 2 can be accurately assigned to the *cis* or *trans* isomers.

Figure 2 shows, moreover, that Boc-Ala-Pro must be present almost exclusively as the *trans* isomer in aqueous solution. From the intensities of the acetylproline resonances it follows that an approximately 1:1 *cis-trans* isomeric equilibrium is set up in aqueous solutions of this compound at room temperature.

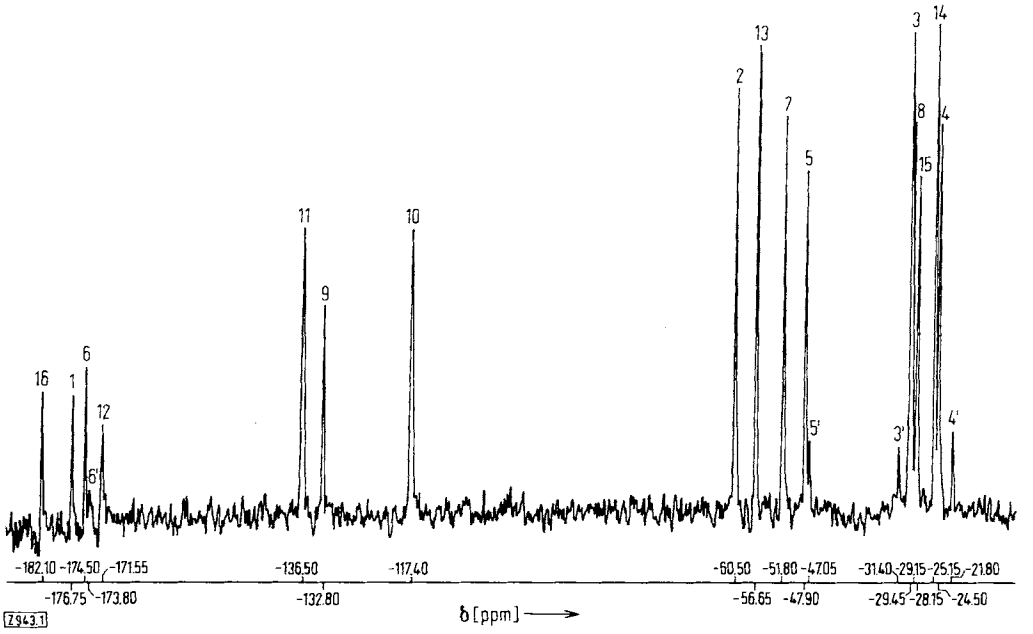


Fig. 1. Pulse Fourier transform (PFT) ^{13}C-NMR spectrum (broad-band proton decoupled, referred to TMS = 0) of TRH, 200 mg in 1.5 ml D_2O, accumulation of 16384 pulse interferograms. 3',4',5',6' see text.

These findings lead to the conclusion that aqueous solutions of TRH contain 10—20% of the *cis* isomer and 90—80% of the *trans* isomer.

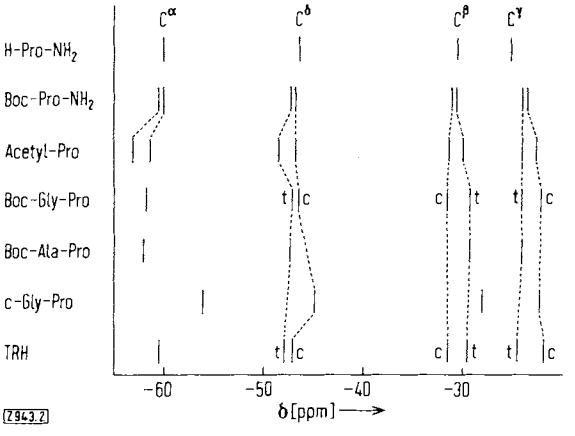


Fig. 2. ^{13}C-NMR line spectra of substituted prolines (referred to TMS = 0). All the values, except those for c-Gly-Pro (DMSO), were determined in water. t = trans, c = cis.

A ^{1}H-NMR investigation of TRH has recently been published[4]. *Cis-trans* isomerism could not be detected, even with a 250-MHz spectrometer.

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[1] *K. Zech*, Dissertation, Universität Tübingen 1973.

[2] *E. Breitmaier, G. Jung*, and *W. Voelter*, Angew. Chem. *83*, 659 (1971); Angew. Chem. internat. Edit. *10*, 673 (1971); *E. Breitmaier* and *W. Voelter*: ^{13}C-NMR Spectroscopy. Verlag Chemie, Weinheim, in press.

[3] *C. M. Deber, F. A. Bovey, J. P. Carver*, and *E. R. Blout*, J. Amer. Chem. Soc. *92*, 6191 (1970).

[4] *S. Fermandjian, P. Pradelles, P. Fromageot*, and *J. Dunand*, FEBS Lett. *28*, 156 (1972).

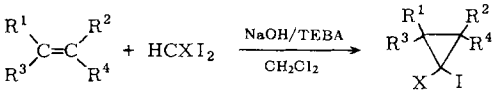
[5] *O. Oster*, Dissertation, Universität Tübingen 1973.

Stable 1,1-Diiodo- and 1-Chloro-1-iodocyclopropanes

By *Rolf Mathias* and *Peter Weyerstahl*[*]

1,1-Diiodocyclopropanes have long been considered as unstable and nonisolable[1]; only their reduction *in situ* to iodocyclopropanes has so far been described[2]. We have now been able to prepare and unequivocally characterize the diiodocyclopropanes *(1)* (Table 1); they were prepared from the corresponding olefins and iodoform by a modified Makosza reaction[3] using CH_2Cl_2 as solvent[4]. Remarkably, the aromatically substituted representatives *(1d)—(1f)* are very much more stable and are formed in higher yields than the aliphatic compounds *(1a)—(1c)*. This could be due to the possibility of electron delocalization in *(1d)—(1f)*. *(1g)* is an exception; however, it should be remembered that *trans*-stilbene reacts only very poorly with dihalocarbenes.

The same reaction with chlorodiiodomethane[5] instead of iodoform affords the even more stable 1-chloro-1-iodocyclopropanes *(2)* in good yields.



(1), X = I; *(2)*, X = Cl

Experimental:

A 50% aqueous solution of sodium hydroxide (50 ml) is added dropwise to a vigorously stirred mixture of haloform (0.1 mol), olefin (0.3 mol), triethylbenzylammonium chloride (TEBA) (0.5 g), and CH_2Cl_2 (100 ml). The final mixture is heated at 50 °C for 3 h and then acidified with dilute sulfuric acid under ice-cooling. The aqueous phase is separated off, extracted with CH_2Cl_2, and the combined organic phases are dried over $MgSO_4$. The dry organic phase is transferred to a refrigerator, and, after removal of solvent, the residue is worked-up as indicated in Table 1.

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Table 1. 1,1-Diiodocyclopropanes *(1)* and 1-chloro-1-iodocyclopropanes *(2)* synthesized from olefins and triiodo- and chlorodiiodomethane.

Cpd.	R^1	R^2	R^3	R^4	Workup [a]	Yield [%]	M.p. [°C] B.p. [°C/torr]	Stability	NMR (CCl_4) TMS = 10, τ	MS [m/e]
(1a)	C_2H_5	H	CH_3	H	D	4	50/0.1	2 weeks at −30 °C	8.91 (3H, t), 8.66 (3H, s), 8.1—8.5 (4H, m),	M (100%), M − C_2H_5 (39%), M − I (40%), M − I_2 (44%)
(1b)	$(CH_3)_3C$	H	H	H	D TLC	[b]	[b]	very unstable, even in solution	8.88 (9H, s), 8.2—8.5 (3H, m)	M (100%), M − I (27%)
(1c)	—$(CH_2)_4$—		H	H	CC	[b]	[b]	very unstable, even in solution	7.5—8.9 (m)	M (2%), CH_2I_2 (100%), M − I (2%)
(1d)	C_6H_5	H	H	H	D [c]	21	80/0.03	>6 months at −30 °C decomposes at 130 °C	7.1—8.0 (3H, ABC), 2.8 (5H, s)	M (4%), M − I (32%), M − I (8%), M − I_2 (100%)
(1e)	4-Cl—C_6H_4	H	H	H	D	59	95/0.07	>4 months at −30 °C undecomposed at 100 °C	7.1—8.1 (3H, ABC), 2.7, 2.9 (1H, A_2B_2)	M (13%), M − Cl (2%), M − I (20%), M − I_2 (100%)
(1f)	C_6H_5	H	C_6H_5	H	CCl_4	20	170	very stable, undecomposed at 185 °C	7.43 (2H, s), 2.5—2.9 (10H, m)	M − I (37%), M − I_2 (77%)
(1g)	C_6H_5	H	H	C_6H_5	CC (CCl_4)	2	102—104	>2 weeks at 20 °C	7.07 (2H, s), 2.7 (10H, s)	M (calc.) 445.9216 (obs.) 445.9121 M − I_2 (86%)
(2a)	C_2H_5	H	CH_3	H	D	65 [d]	50/2	>3 months at −30 °C	8.95, 8.94 (3H, t), 8.70, 8.69 (3H, s), 8.2—8.6 (4H, m)	M (5%), M − C_2H_5 (13%), CHClI (100%), M − I (10%)
(2b)	$(CH_3)_3C$	H	H	H	D	56 [d]	55/0.3	3 months at −30 °C	8.85, 8.83 (9H, s), 8.7—9.1 (3H, s)	M (0.4%), CHClI (100%), M − I (0.3%)
(2c)	—$(CH_2)_4$—		H	H	D	53 [d]	55/0.2	2 weeks at −30 °C	7.5—9.0 (m)	M (36%), M − C_3H_6 (100%), M − I (30%)
(2d)	C_6H_5	H	H	H	D	49 [d]	55/0.2	>3 months at 20 °C	6.9—8.3 (3H, ABC), 2.8 (5H, s)	M (9%), M − I (42%), M − HI—Cl (100%)
(2e)	4-Cl—C_6H_4	H	H	H	CC	[b]	[b]	2 weeks at −30 °C, resinfies rapidly in air	6.9—8.3 (3H, ABC), 2.6—2.9 (4H, m)	M (19%), M − Cl (5%), M − I (83%), M − HI—Cl (51%)
(2f)	C_6H_5	H	C_6H_5	H	CCl_4	59	140	very stable, undecomposed at 170 °C	7.73 (2H, AB), 7.67 (J = 7 Hz), 2.5—2.9 (10H, m)	M (0.5%), M − I (100%), M − I − Cl (100%)

[a] D = flask distillation, TLC = thin-layer chromatography, CC = column chromatography on Al_2O_3; CCl_4 = recrystallization from CCl_4.
[b] Not determinable.
[c] After freezing out from HCl_3 or polymer with petroleum ether at −30 °C.
[d] Isomeric mixture.

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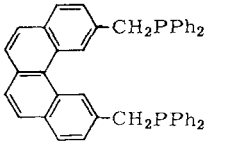
[1] *W. Kirmse:* Carbene, Carbenoide und Carbenanaloge. Verlag Chemie, Weinheim 1969, p. 112, 197.
[2] *J. P. Oliver* and *V. V. Rao*, J. Org. Chem. *31*, 2696 (1966).
[3] *M. Makosza* and *M. Wawrzyniewicz*, Tetrahedron Lett. *1969*, 4659.
[4] *P. Weyerstahl, R. Mathias*, and *G. Blume*, Tetrahedron Lett. *1973*, 611.
[5] *J. Hine*, J. Amer. Chem. Soc. *80*, 824 (1958).

Square Planar Transition Metal Complexes with a Bidentate Ligand Spanning *trans*-Positions[***]

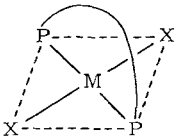
By *N. J. DeStefano, D. K. Johnson*, and *L. M. Venanzi*[*]

Although there are a very large number of square planar complexes containing bidentate ligands[1], there appears to be only one well-established example of a compound in which the organic ligand spans *trans*-positions, *i.e.* $[NiBr_2\{(C_6H_{11})_2P(CH_2)_5P(C_6H_{11})_2\}]$[2].

In the course of a study of square planar complexes, we have prepared[3] the bidentate ligand 2,11-bis(diphenylphosphinomethyl)benzo[*c*]phenanthrene *(1)*. Molecular models indicate that this ligand should promote the formation of square planar complexes in which the two phosphorus atoms span *trans*-positions.



(1)



(2)

(2) = *trans*-$[MX_2(1)]$: M = Ni; X = Cl, Br, I, NCS
M = Pd; X = Cl, Br, I
M = Pt; X = Cl, I

The reaction of a suitable substrate, *e.g.* NiX_2, $[PdX_2(PhCN)_2]$, $Na_2[MX_4]$, *etc.*, with ligand *(1)* gives complexes of type *(2)*, *trans*-$[MX_2(1)]$.

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[***] First presented at the 163rd ACS National Meeting, Boston, Mass., April 10—14, 1972. We thank the National Science Foundation for the support of this work, Matthey-Bishop, Inc., for a loan of platinum metal salts, Dr. *R. M. Lane* for carrying out some preliminary experiments, and Dr. *P. S. Pregosin* for much valuable assistance with the NMR measurements.

Satisfactory analytical data were obtained for all the above compounds. These are monomeric and non-electrolytes in dichloromethane solution. The *trans*-configuration of the phosphorus atoms in complexes *(2)* is established by their NMR spectra:

(i) The ^{31}P-NMR spectrum of $[PtCl_2(1)]$ shows a value of $^1J_{(^{195}Pt-^{31}P}$ of 2579 Hz (as compared with values of 3731 and 2584 Hz for *cis*- and *trans*-$[PtCl_2(Ph_2PCH_2Ph)_2]$[4], respectively, in agreement with previously published data for complexes of this type[5].

(ii) The ^{1}H-NMR spectra of all the complexes of type *(2)* examined to date appear in the form of 1:2:1-triplets and it has been shown[5] that such multiplets are indicative of *trans*-configuration[6].

As complexes $[NiX_2(Ph_2PCH_2Ph)_2]$ (X = Br or I) give mixtures of tetrahedral and square planar species[7] and complexes $[NiX_2(Ph_2P(CH_2)_5PPh_2)]$ (X = Br or I) have tetrahedral structure[8], the fact that ligand *(1)* forms only square planar complexes with nickel(II) provides confirmation for the hypothesis, based on studies of molecular models, that this ligand does indeed promote the formation of square planar species.

It is interesting to note that, while the ligand $(C_6H_{11})_2P(CH_2)_5P(C_6H_{11})_2$ reacts readily with cobalt(II) halides to give tetrahedral complexes of the type $[CoX_2L]$[2], compound *(1)* does not appear to react with cobalt(II) salts. This is not unexpected as molecular models show that there would be severe overlap of the terminal benzene rings if ligand *(1)* were to form tetrahedral complexes. This ligand, however, does react with substrates containing Co^I, Rh^I, Ir^I or Ag^I and the products obtained are under investigation.

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[1] For a review of complexes with bidentate phosphanes see: *W. Levason* and *C. A. McAuliffe*, Advan. Inorg. Chem. Radiochem. *14*, 173 (1972).

[2] *K. Issleib* and *G. Hohlfeld*, Z. Anorg. Allg. Chem. *312*, 170 (1961).

[3] *N. J. DeStefano, D. K. Johnson, R. M. Lane*, and *L. M. Venanzi*, to be published; *R. M. Lane*, Ph. D. Thesis, State University of New York at Albany, 1971.

[4] *N. J. DeStefano, D. K. Johnson, P. S. Pregosin*, and *L. M. Venanzi*, to be published.

[5] *J. F. Nixon* and *A. Pidcock*, Annu. Rev. NMR Spectrosc. *2*, 345 (1969).

[6] This criterion has been criticized on the grounds that $^2J_{P\text{-}P}$ in some *cis*-complexes is sufficiently large to give rise to triplets [*J. G. Verkade*, Coord. Chem. Rev. *9*, 1 (1972) and references therein]. However, as the methylenic protons in the square planar complexes *trans*-$[MX_2(Ph_2PCH_2Ph)_2]$ give rise to triplet patterns while those of the *cis*-isomers give the expected doublets, it is felt that the above geometrical assignments are correct.

[7] *M. C. Browning, J. R. Mellor, D. J. Morgan, S. A. J. Pratt, L. E. Sutton*, and *L. M. Venanzi*, J. Chem. Soc. *1962*, 693; *B. T. Kilbourn, H. M. Powell*, and *J. A. C. Darbyshire*, Proc. Chem. Soc. London *1963*, 207; *B. T. Kilbourn* and *H. M. Powell*, J. Chem. Soc. *A 1970*, 1688.

[8] *L. Sacconi* and *J. Gelsomini*, Inorg. Chem. *7*, 291 (1968).

A Phosphorus(v) Derivative Having Coordination Number 3: Bis(trimethylsilyl)aminobis(trimethylsilylimino)phosphorane[**]

By *Edgar Niecke* and *Wilhelm Flick*[*]

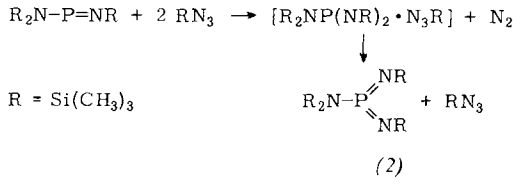
The question of the existence of phosphorus(v) stabilized by p_π-p_π bonding (see *(1a, b)*) has been under study for some time. Thus the intermediacy of such species has been postulated in oxidative phosphorylation, oxidation of perfluoroacylphosphanes, and the hydrolysis of *N*-monoalkylphosphoramidates, organomono- and diphosphates[1], and invoked in enzymatic and nonenzymatic transphosphorylations[2] without any such compound actually having been isolated to date[3].



(1a) *(1b)*

Since the synthesis of the first phosphabenzenes[4] established the existence of phosphorus(III) compounds having coordination number 2, it was to be expected that, given suitable substituents, the oxidized form with P^V and coordination number 3 should be stable and detectable by spectroscopy.

Starting from the synthesis of phosphazene from phosphanes and azides, we treated bis(trimethylsilyl)aminotrimethylsilyliminophosphane[5] with trimethylsilyl azide[6]. The reaction proceeds with liberation of N_2 at room temperature, giving initially a phosphorane-silyl azide adduct[7] which decomposes above 100 °C to form the diiminophosphorane *(2)*.



(2)

Bis(trimethylsilyl)aminobis(trimethylsilylimino)phosphorane *(2)* is an extremely hygroscopic crystalline solid which can be distilled without decomposition in a vacuum: m. p. 36 °C, b. p. 95 °C/0.1 torr. Its composition and monomeric structure were established by elemental analysis, cryoscopic molecular-weight determination, and mass, NMR (^{1}H, ^{29}Si, ^{31}P), and IR spectra.

Apart from the molecular ion [*m/e* (rel. int.)] 365 (9%), the mass spectrum contains the following characteristic fragments of higher mass numbers: $M-CH_3$ 350 (100%); $M-2CH_3$ 335 (3%); $M-Si(CH_3)_3$ 292 (3%); $M-NSi(CH_3)_3$ 278 (2%); $M-Si(CH_3)_3$, CH_3 277 (3%).

In the ^{1}H-NMR spectrum (50% solution in C_6H_{12}; TMS internal) two silyl proton signals of equal intensity appear at room temperature, that at higher field belonging to the silylimino groups. This signal shows the expected doublet structure at high resolution[8]. A reversible exchange leading to equilibrium between silylamino and silylimino protons[9] at 90—95 °C could be detected by high-temperature measurements. Silylimino H: $\delta = -0.11$ ppm (d), $^4J_{HP} = 0.65$ Hz; silylamino H: $\delta = -0.32$ ppm; $\Delta G_c^{\neq} = 19.0$—19.3 kcal/mol (neat sample; 60 MHz).

The ^{29}Si-NMR spectrum (70% solution in TMS[10]) indicates two differently bonded silicon atoms in agreement with the proton spectrum. As expected the amount of ^{29}Si—^{31}P interaction is greater for the silylimino groups observed at higher field. Silylimino Si: $\delta = 8.0$ ppm, $^2J_{SiH} = 6.8$, $^2J_{SiP} = 16.7$ Hz; silylamino Si: $\delta = -9.4$ ppm, $^2J_{SiH} = 6.7$, $^2J_{SiP} = 1.2$ Hz.

In the ^{31}P-NMR spectrum (70% solution in C_6H_{12}; H_3PO_4 external) the unusual electronic situation of the phosphorus in *(2)* is reflected in a downfield signal shift compared to iminophosphoranes of coordination number 4[11]: $\delta = -55.0$ ppm.

IR spectrum (range 1500—600 cm^{-1}, tentative assignment): ≈ 1435 sh, ≈ 1415 sh, 1390 m all $\delta_{as}CH_3$; 1332 s, br $\nu_{as}P{=}N$;

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≈1275 sh, 1248 vs both $\delta_s CH_3$; 1018 m $\nu_s P{=}N$; 945 s, br $\nu_{as}NSi_2$; 9.15 νPN; ≈865 sh, 838 vs, ≈830 sh all $\rho_{as}CH_3$; 772 m, 756 m both $\rho_s CH_3$; 685 m, ≈675 sh, 639 m, 610 m-w all νSiC. Comparison of $\nu_{as,s}(P{=}N)$ with the value for a "pure" P=N stretching vibration of 1210—1220 cm^{-1}[12] suggests that contributions from the polar resonance structure

$$[(CH_3)_3Si]_2N-\overset{\oplus}{P}[=\overset{\ominus}{N}Si(CH_3)_3]_2$$

must also be taken into consideration in descriptions of the bonding in *(2)*[13].

The chemistry of the phosphorane *(2)* is largely determined by the considerable electrophilic character of the phosphorus. Thus, *e.g.*, alcohols undergo ready addition to form the corresponding monophosphazenes *(3)*.

$$(2) + HOR \longrightarrow R_2N-\underset{\displaystyle HNSiR_3}{\overset{\displaystyle OR}{P}}=NSiR_3$$

R = CH_3 *(3)*

(3): yield 70%. IR: ν(P=N) = 1335; ν(PO—R) = 1182; ν(P—OR), ν_{as}(PNSi) = 1092, 1062 cm^{-1}. ^{31}P-NMR: δ = −1.8 ppm, $^3J_{HP}$ = 11.8 Hz.

Experimental:

$(CH_3)_3SiN_3$ (15 g, 0.13 mol) is added dropwise with stirring to $[(CH_3)_3Si]_2NPNSi(CH_3)_3$ (14 g, 0.05 mol) at 40 °C in a 100 ml two-neck flask fitted with a dropping funnel and a reflux condenser; the reaction mixture evolves N_2 and warms up to about 50 °C. After evolution of gas has ceased, stirring is continued for 2 to 3 h and unreacted silyl azide then drawn off. The solid residue is fractionated by molecular distillation at 100—120 °C, the phosphorane distilling over at 95 °C/0.1 torr. Renewed distillation affords 12 g (65%) of pure product.

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[1] *R. F. Hudson:* Structure and Mechanism in Organo-Phosphorus Chemistry. Academic Press, New York 1965; *A. J. Kirby* and *S. G. Warren:* The Organic Chemistry of Phosphorus. Elsevier, Amsterdam 1967; *A. F. Gerrard* and *N. K. Hamer*, J. Chem. Soc. *B 1968*, 539; *D. L. Miller* and *T. Ukena*, J. Amer. Chem. Soc. *91*, 3050 (1969); *E. Lindner, H. D. Ebert, K. Geibl*, and *A. Haag*, Chem. Ber. *104*, 3121 (1971); *D. G. Gorenstein*, J. Amer. Chem. Soc. *94*, 2523 (1972).

[2] *T. C. Bruice* and *S. Benkovic:* Bioorganic Mechanisms. Benjamin, New York 1966.

[3] Experimental proof has recently been obtained for the intermediate formation of a monomeric alkyl metaphosphate in the gaseous phase: *F. H. Westheimer*, personal communication.

[4] *G. Märkl*, Angew. Chem. *78*, 907 (1966); Angew. Chem. internat. Edit. *5*, 846 (1966).

[5] *E. Niecke* and *W. Flick*, Angew. Chem. *85*, 586 (1973); Angew. Chem. internat. Edit. *12*, 585 (1973).

[6] *L. Birkofer, A. Ritter*, and *P. Richter*, Angew. Chem. *74*, 293 (1962); Angew. Chem. internat. Edit. *1*, 267 (1962); *N. Wiberg, F. Raschig*, and *R. Sustmann, ibid. 74*, 388 (1962); *1*, 335 (1962).

[7] Subject to a detailed examination, we consider the intermediate formation of a phosphorane-silyl azide to be highly probable on the basis of spectroscopic evidence.

[8] *W. Wolfsberger, H. H. Pickel*, and *H. Schmidbaur*, Z. Naturforsch. *24b*, 979 (1971); and further literature cited therein.

[9] *O. J. Scherer*, Angew. Chem. *81*, 871 (1969); Angew. Chem. internat. Edit. *8*, 861 (1969); cf. also *O. J. Scherer* and *R. Thalacker*, Z. Naturforsch. *27b*, 1429 (1972) and [5].

[10] The noise decoupled PFT ^{29}Si-NMR spectrum was measured on a 70% solution in C_6F_6.

[11] *M. M. Crutchfield, D. H. Dungan, L. H. Letcher, V. Mark*, and *J. R. Van Wazer*, Top. Phosphorus Chem. *5*, 391 (1967); *M. Bermann, ibid. 7*, 325 (1972).

[12] *W. Wiegräbe* and *H. Bock*, Chem. Ber. *101*, 1414 (1968).

[13] A crystal structure analysis is in progress.

X-Ray Structure Analysis of the Triple-Decker Sandwich Complex Tris(η-cyclopentadienyl)dinickel Tetrafluoroborate

By *Erich Dubler, Marcus Textor, Hans-Rudolf Oswald*, and *Albrecht Salzer*[*]

We have performed an X-ray structure analysis on the complex $[Ni_2(C_5H_5)_3]BF_4$ recently synthesized by *Werner* and *Salzer*[1, 2] in order to confirm the "triple-decker sandwich" structure proposed on the basis of chemical properties and NMR spectra.

The single crystals prepared from a solution in propionic anhydride are orthorhombic: space group $P2_12_12_1$; $a = 17.019(2)$, $b = 11.454(2)$, $c = 8.074(1)$ Å; $d_{exp} = 1.66$, $d_{calc} = 1.69\ g\,cm^{-3}$; $Z = 4$. A total of 1216 independent reflections (180 not observed, $I \leqslant 3\ \sigma_I$; $2\theta \leqslant 45°$; $\theta/2\theta$ scan) were recorded on a Picker FACS 1 diffractometer with $Mo_{K\alpha}$ radiation.

The positions of the Ni atoms could be determined from Patterson syntheses. A series of consecutive least-squares refinements and difference Fourier syntheses revealed the positions of the C, B, and F atoms. It became apparent that assumption of fixed geometry of the rings, particularly with regard to twisting in the plane of the ring, led to an incomplete description of the positions of the C atoms in the three crystallographically distinct cyclopentadienyl ligands ("cp rings").

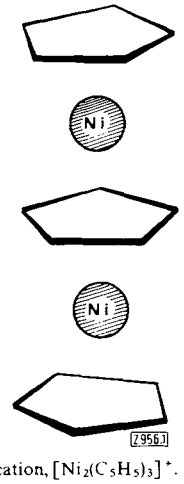


Fig. 1. Structure of the tris(η-cyclopentadienyl)dinickel cation, $[Ni_2(C_5H_5)_3]^+$.

This is probably due less to true thermal vibrations than to characteristic disorder phenomena in the crystals. Refinement converged to a value of $R = 6.3\%$.

The structure of the complex cation $[Ni_2(cp)_3]^+$, as shown in Figure 1, agrees essentially with the proposed triple-decker sandwich structure[1]. Neglecting the observed disorder with regard to twisting in the ring plane, the cp ring atoms are depicted in an idealized manner (most probable positions from difference Fourier syntheses).

The average distances between the Ni atoms and the C atoms of the two terminal cp rings are 2.09 and 2.08 Å, whereas

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values of 2.13 and 2.16 Å were found for the average Ni—C distances to the bridging cp ring; the distances from the Ni atoms to the centers of the rings are found to be: outer cp rings 1.745 and 1.711 Å, inner cp ring 1.771 and 1.805 Å.

The findings that the metal —C distances to the two terminal cp rings are shorter than to the bridging cp ring accords well with the picture obtained from the substitution reactions of the $[Ni_2(cp)_3]^+$ ion with Lewis bases[3].

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revised: October 12, 1973 [Z 956 IE]
German version: Angew. Chem. 86, 125 (1974)

[1] *H. Werner* and *A. Salzer*, Synth. Inorg. Metal-org. Chem. *2*, 239 (1972).

[2] *A. Salzer* and *H. Werner*, Angew. Chem. *84*, 949 (1972); Angew. Chem. internat. Edit. *11*, 930 (1972).

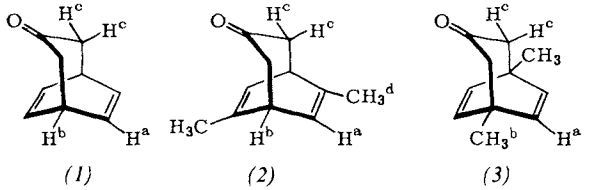
[3] *A. Salzer* and *H. Werner*, Synth. Inorg. Metal-org. Chem. *2*, 249 (1972).

Simple Synthesis of Bicyclo[3.2.2]nona-6,8-dien-3-ones from Arenes[**]

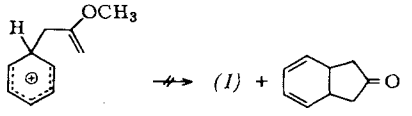
By *H. M. R. Hoffmann* and *A. E. Hill*[*]

Dedicated to Professor Heinrich Hellmann on the occasion of his 60th birthday

We have found a simple one-stage transformation of benzene into bicyclo[3.2.2]nona-6,8-dien-3-one *(1)*, which uses the silver salt promoted reaction with 2-methoxyallyl bromide[1] and proceeds at room temperature. After work-up with dilute acid one isolates 1-phenyl-2-propanone and *(1)*, m.p. 56 °C, IR (CCl_4) 1698 cm^{-1}, NMR (CCl_4)[2]: $\delta = 6.2$—6.4 (m, $4H^a$), 3.1—3.4 (br m, $2H^b$), 2.35 ppm (d, $4H^c$, $J \approx 4$ Hz)[3].



(1) *(2)* *(3)*



(4) *(5)*

The analogous reaction with *p*-xylene afforded *p*-xylylacetone (0.54 g, 10%) and the 6,8-dimethyl derivative *(2)* (0.19 g, 3.5%)[4], IR (CCl_4): 1695 cm^{-1}, NMR (CCl_4): $\delta = 5.7$—6.0 (complex d, $2H^a$), 2.7—3.0 (br m, $2H^b$), 2.28, 2.32 ($4H^c$), 1.80 (d, $6H^d$, $J = 1.4$ Hz)[3]. As a minor bicyclic isomer [*(2)* : *(3)* = 3.5 : 1] the symmetric 1,5-dimethyl derivative *(3)* was isolated. NMR (CCl_4): $\delta = 5.92$ (s, $4H^a$), 1.32 (s, $6H^b$), 2.20 (s, $4H^c$)[3]. Toluene reacted in similar fashion.

Since dihydroindanones as, *e.g.*, *(5)* in the case of benzene, are not formed under our conditions, we suggest that the bicyclics described arise in a concerted cycloaddition rather than stepwise *via* the conventional cyclohexadienyl cation *(4)*, the exclusive formation of which might have been expected in the reaction of benzene with a carbenium ion or electrophile[5].

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[**] We thank the Science Research Council for selective support in the field of organometallic chemistry.

Interestingly, bicyclo[3.2.2]nona-6,8-dien-3-ones are sensitive to acid, which is liberated throughout the silver trifluoroacetate induced reaction. In neat deuteriotrifluoroacetic acid the parent bicyclic *(1)* was cleanly transformed into phenylacetone after 3 h at room temperature. While this cleavage will lower the yields, it is clear that a range of new and interesting bicyclics has now become readily accessible.

Bicyclo[3.2.2]nona-6,8-dien-3-one (1)

Benzene (40 ml) and 2-methoxyallyl bromide[6] (5 g, 33 mmol) are diluted with isopentane (100 ml) and mixed with Na_2CO_3 (2 g). The resulting suspension is stirred with a vibromixer (100 cps), while a mixture of silver trifluoroacetate (10 g, 46 mmol) and Na_2CO_3 (4 g) is added in small portions at room temperature over a period of 9 h. The reaction mixture is stirred for a further 16 h in the dark and then worked up by careful addition of nitric acid (10%, 100 ml), evaporation of the bulk of isopentane, and extraction of the resulting suspension with $CHCl_3$ (3×100 ml). The combined organic layer is washed with water, dried, and the solvent removed. A yellow oil is obtained; preparative glc (carbowax 20M, 206 °C) affords 1-phenyl-2-propanone (0.89 g, 20%) as a colorless oil and bicyclo[3.2.2]-nona-6,8-dien-3-one *(1)* (0.27 g, 6%; work-up by fractional distillation gave a yield of 11%).

Received: October 15, 1973 [Z 960 IE]
German version: Angew. Chem. 86, 127 (1974)

[1] *A. E. Hill, G. Greenwood*, and *H. M. R. Hoffmann*, J. Amer. Chem. Soc. *95*, 1338 (1973); see also *H. M. R. Hoffmann*, Angew. Chem. *85*, 877 (1973); Angew. Chem. internat. Edit. *12*, 918 (1973).

[2] We thank Dr. *A. J. Baker* for sending us the NMR spectrum of *(1)*; see *A. J. Baker, A. M. Chalmers, W. W. Flood, D. D. MacNicol, A. B. Penrose*, and *R. A. Raphael*, Chem. Commun. *1970*, 166.

[3] The mass spectrum is in agreement with the quoted structure.

[4] Yield after isolation by preparative gas-liquid chromatography.

[5] Some polyalkylbenzenes give a minor amount of substituted 1,4-cyclohexadiene on nitration in solvent acetic anhydride: *A. Fischer* and *J. N. Ramsay*, J. C. S. Perkin II *1973*, 237, and references therein; see also *P. C. Myhre*, J. Amer. Chem. Soc. *94*, 7921 (1972); *J. H. Ridd*: Studies on Structure and Reactivity. Methuen, London 1966, p. 133.

[6] *G. Greenwood* and *H. M. R. Hoffmann*, J. Org. Chem. *37*, 611 (1972).

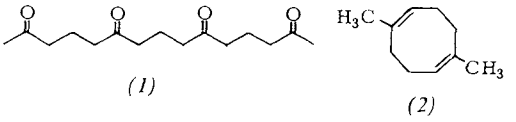
Synthesis of 2,6,10,14-Pentadecanetetrone, a δ-Tetraketone ("Harries' Tetraketone")

By *Burchard Franck, Volker Scharf*, and *Marieluise Schrameyer*[*]

After hydrolysis of 1706 g of the ozonide of a caoutchouc sample previously subjected to partial isomerization by addition of HCl and subsequent dehydrohalogenation, *Harries*[1] succeeded, in 1914, in isolating a 0.05% yield of a tetraketone $C_{15}H_{24}O_4$ (m. p. 123 °C) which he suspected to have the structure *(1)*[2]. This "Harries' tetraketone", although of unproven structure, permitted the dramatic disproof of the cyclic formula of caoutchouc *(2)* in favor of a higher molecular formula[1]. Moreover, if the compound really is the 2,6,10,14-pentadecanetetrone *(1)*, it represents the highest known member in the series of poly-δ-carbonyl compounds whose importance as synthetic and biosynthetic precursors[3–6] arises from their ability to undergo diverse intramolecular condensations. We have now been able to prepare the highly reactive δ-tetraketone *(1)*, to establish its identity with Harries' tetraketone, and to convert it into condensation products.

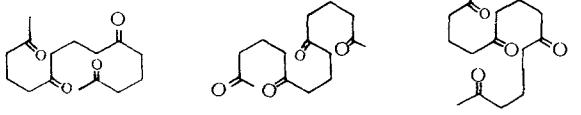
[*] Prof. Dr. B. Franck, Dr. V. Scharf, and Dipl.-Chem. M. Schrameyer
Organisch-Chemisches Institut der Universität
44 Münster, Orléans-Ring 23 (Germany)

Some of the possible ring closure reactions of the tetraketone *(1)* are suggested by the conformations *(1a)*—*(1c)*. Owing to the reactivity of *(1)* the synthetic pathway chosen involved



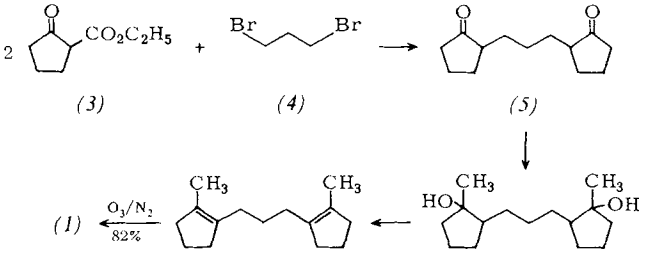
(1)

(2)



(1a) *(1b)* *(1c)*

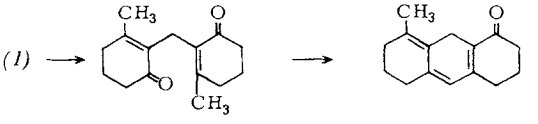
introduction of the four keto groups in the last step by ozonolysis of a diolefin *(6)*. Thus attention was focused on the hitherto unreported compound 1,3-bis-(2-methyl-1-cyclopentenyl)propane *(6)* as key intermediate[7]. Condensation of the potassium salt of ethyl 2-oxocyclopentanecarboxylate *(3)* with 1,3-dibromopropane *(4)* in boiling toluene and subsequent hydrolysis and decarboxylation of the product (2% HI, 100 °C, 120 h)[8] yielded 2,2'-trimethylenedicyclopentanone *(5)* in 34% yield based on *(3)*. Compound *(5)* was converted into the diol *(7)* (89%) which yielded a dominant proportion of the desired compound *(6)*, alongside the five other possible isomers, on dehydration (boiling with benzene/*p*-toluenesulfonic acid).



(3) *(4)* *(5)* *(1)* *(6)* *(7)*

Compound *(6)* was obtained as the analytically pure isomer (GC, NMR) by microdistillation over a spinning band column (Normag 8101): b.p. 78 °C/0.01 torr; yield 60% based on diol. Its ^{1}H-NMR spectrum contains a singlet at $\tau = 8.40$ ($2CH_3$) but no signal due to an olefinic proton. In the mass spectrum the molecular ion (54%) is accompanied by the fragments C_8H_{12} (100%), C_7H_9 (72%), and C_6H_7 (39%) formed by allylic cleavage and loss of methyl as the most intense peaks. Ozonolysis of the diene *(6)* with O_2-free ozone (ozone desorbed from a silica gel cold trap at −80 °C with N_2[10]) in methanol/methylene chloride at −20 °C and subsequent catalytic hydrogenolysis afforded an 82% yield of 2,6,10,14-pentadecanetetrone *(1)* which crystallized as colorless platelets of m.p. 123 °C, as reported by *Harries*[1]; IR (KBr): 1715 cm^{-1} (C=O). The ^{1}H-NMR spectrum ($CDCl_3$) shows three resonances at $\tau = 7.67$ (12H), 7.98 (6H), and 8.24 (6H) for CH_2—CO, CH_3—CO, and central CH_2 between two CO groups respectively. The mass spectrum is characterized by a very small $M^{\oplus}$ peak (*m/e* 268) and numerous other fragments, some of which are formed by McLafferty rearrangement.

Having established the structure *(1)* for Harries' tetraketone, we proceeded to investigate its acid- and base-catalyzed condensation and found the linear annelating conformation *(1a)* to be product-determining. Thus the action of concentrated sulfuric acid (20 °C, 2 h) or BF_3-ether/methylene chloride (40 °C, 40 h) gave 3,3'-dimethyl-2,2'-methylenedicyclohexenone *(8)* in 25 and 12% yield respectively; m.p. 25—27 °C (colorless needles); ^{1}H-NMR ($CDCl_3$): $\tau = 8.04$ (s, $2CH_3$); 6.66 (s, bridging CH_2); MS: *m/e* 232 ($M^{\oplus}$, 100%); 217 ($M^{\oplus} - CH_3$, 45%); 189 ($M^{\oplus} - C_3H_7$; 31%); 176 ($M^{\oplus} - CH_2CH_2CO$, 60%); IR (KBr): 1670 cm^{-1} (C=O). Heating in 2.5 N NaOH (95 °C, 45 min) converts *(1)* in 37% yield, and likewise *(8)*, into a deep yellow product whose mode of formation and spectroscopic data show it to be 8-methyl-1,2,3,4,5,6,7,9-octahydro-1-anthracenone *(9)*; UV ($CHCl_3$): $\lambda_{max} = 355$ nm; ^{1}H-NMR



(1) *(8)* *(9)*

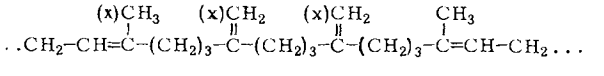
($CDCl_3$): $\tau = 8.21$ (s, CH_3); 4.21 (s, =CH—); IR (KBr): 1660 cm^{-1} (C=O); semicarbazone: m.p. 180 °C (pale yellow needles); MS: *m/e* 271 ($M^{\oplus}$, 71%); 254 ($M^{\oplus} - CH_3$, 79%); 228 ($M^{\oplus}$ − HNCO, 76%).

Received: November 22, 1973 [Z 961 IE]
German version: Angew. Chem. *86*, 160 (1974)

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[1] *C. Harries*, Liebigs Ann. Chem. *406*, 173 (1914).

[2] *(1)* can be formed from a partial structure of the caoutchouc chain resulting on isomerization at three adjacent methyl groups (×):



[3] *H. O. House*: Modern Synthetic Reactions. Benjamin, Menlo Park, Calif. 1972, p. 606.

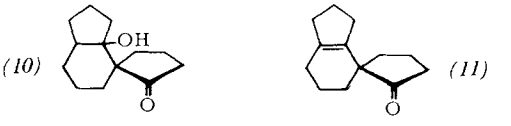
[4] *S. Danishefsky* and *B. H. Migdalof*, J. Amer. Chem. Soc. *91*, 2807 (1969).

[5] Cf. the Robinson annelation: *E. C. du Feu*, *F. J. McQuillin*, and *R. Robinson*, J. Chem. Soc. *1937*, 53; *J. H. Brewster* and *E. L. Eliel*, Org. React. 7, 99 (1953).

[6] *E. Leete* and *J. O. Olson*, Chem. Commun. *1970*, 1651.

[7] *R. E. Ireland*: Organic Synthesis. Prentice-Hall, Englewood Cliffs, N. J. 1969.

[8] Hydrolysis and decarboxylation of the bis(β-keto acid ester) formed from *(3)* and *(4)* is greatly opposed by the non-coplanar arrangement of the carbonyl and carboxy group and by the tendency of *(5)* to undergo intramolecular aldol condensation forming the spiro ketone *(10)*. Both lithium iodide dihydrate [9] and other hydrolysis and decarboxylation reagents afforded only *(10)* and its dehydration product *(11)*.



(10) *(11)*

[9] *A. Eschenmoser*, *J. Schreiber*, and *F. Elsinger*, Helv. Chim. Acta *43*, 113 (1960).

[10] *G. Hesse* and *E. Bayer*, Z. Naturforsch. *19b*, 875 (1964).

The Synthesis of Tetradehydrocyclotetradeca[*c*]furans ("Didehydro[14]annuleno[*c*]furans"), 18 π-Electron Analogs of Isobenzofuran[1][****]

By *Philip J. Beeby*, *Rex T. Weavers*, and *Franz Sondheimer*[*]

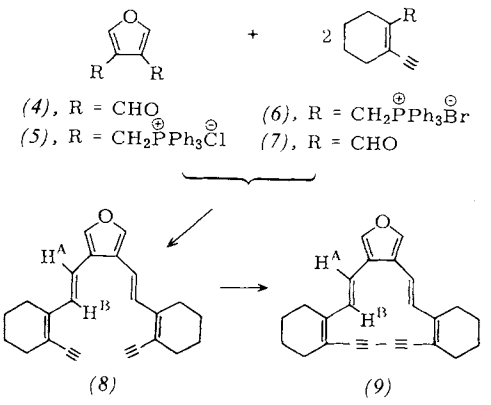
An interesting group of compounds results from the fusion of furan at the 3,4-position to fully unsaturated carbocycles. Examples are the $4n$ π-electron systems cyclobuta[*c*]furan *(1)*[2] and cycloocta[*c*]furan *(3)*[3], and the $(4n+2)$ π-electron system isobenzofuran *(2)*[4]. We now report the synthesis



(1) *(2)* *(3)*

of the two first macrocyclic examples of this series, the $(4n+2)$ π-electron systems 10,11,12,13-tetradehydro-6,7,8,9,14,15,16,17-octahydrodibenzo[6,7:12,13]cyclotetradeca[*c*]furan *(9)* and 7,12-dimethyl-8,9,10,11-tetradehydrocyclotetradeca[*c*]furan *(12)*.

Wittig reaction of 3,4-furandicarboxaldehyde *(4)*[5,6] and two molar equivalents of the phosphonium salt *(6)*[7] in dimethylformamide with ethanolic lithium ethoxide at 80 °C led to *ca.* 30% of the unstable liquid di-*trans* compound *(8)*. This substance could also be obtained, though only in *ca.* 10% yield, by the Wittig reaction of the bis(phosphonium) salt *(5)*[6] and the aldehyde *(7)*[8] at 95 °C. Oxidative coupling of *(8)* with cupric acetate in pyridine at 70 °C under relatively dilute conditions, rigorously excluding oxygen, then yielded 50% of the tetradehydrocyclotetradeca[*c*]furan ("didehydro-[14]annuleno[*c*]furan"[*****]) *(9)* as yellow needles, which decomposed on attempted melting point determination [*m/e* 326.166 (calcd. 326.167); λ_{max} (ether) *ca.* 265 sh (ε 13200), *ca.* 280 sh (21000), 300 (39900), and 382 nm (3500)[9]].



Substances related to *(9)* have been shown to exhibit conformational mobility[10] and the position of the olefinic protons H^A and H^B (external or internal) was unknown. It was therefore decided to prepare the corresponding dimethyl compound *(12)*, in which the olefinic protons H^C must be external. The dimethyl series is also preferable since the methyl ^{1}H-NMR resonances are sharp singlets (see Ref. [1]), whereas the allylic proton resonances in the cyclohexene series [*e.g.*, in *(8)* and *(9)*] are rather broad multiplets.

Reaction of the bis(phosphonium) salt *(5)* with two molar equivalents of *n*-butyllithium in tetrahydrofuran at −70 °C gave the corresponding bis(ylide), which was then treated with two molar equivalents of *cis*-3-methyl-2-penten-4-ynal *(10)*[11] (−15 to 20 °C)[12]. This reaction resulted in *ca.* 15% of the di-*trans* compound *(11)* as plates, m.p. 75—78 °C (decomp.) [*m/e* 248.119 (calcd. 248.120); λ_{max} (ether), 285 (ε 24600) and 310 nm (25800)]. Coupling of *(11)* with cupric acetate in pyridine, as before, then gave the tetradehydrocyclotetradeca[*c*]furan ("didehydro[14]annuleno[*c*]furan") *(12)* in 25—30% yield as yellow needles, which decomposed on attempted melting point determination [*m/e* 246.101 (calcd. 246.105); λ_{max} (ether) *ca.* 265 sh (ε 7200), *ca.* 275 sh (10700), 301 (17500), and 395 nm (1900)[9]].

Table 1. ^{1}H-NMR parameters of *(8)* and *(9)* (at 60 MHz) and *(11)* and *(12)* (at 100 MHz) in $CDCl_3$ (τ-values, internal standard TMS, *J* in Hz).

	(8) [a]	*(9)*	Δ *(9)*—*(8)*	*(11)* [b]	*(12)*	Δ *(12)*—*(11)*
Furan-H	2.50 s	2.28 s	−0.22	2.47 s	2.18 s	−0.29
H^A	3.28 d	3.21 d	−0.07	3.56 d	3.48 d	−0.08
J	16	16		16	16	
H^B	2.70 d	3.54 d	+0.84	3.03 dd	3.69 dd	+0.66
J	16	16		16,12	16,10	
H^C	—	—	—	3.62 d	3.28 d	−0.34
J	—	—		12	10	
Allylic H	7.7 m	7.6 m	−0.1	—	—	—
Nonallylic H	8.3 m	8.3 m	0	—	—	—
CH_3	—	—	—	8.02 s	7.94 s	−0.08

[a] In addition, a singlet at τ = 6.76 (≡CH).
[b] In addition, a singlet at τ = 6.70 (≡CH).

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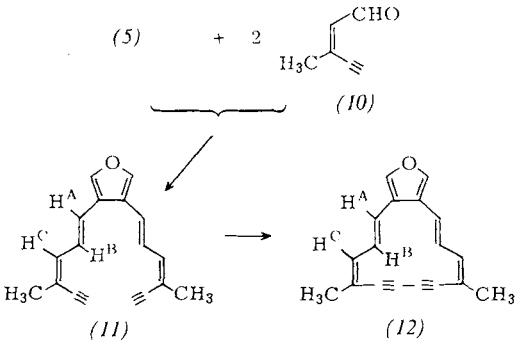
[***] Present address: Chemistry Department, University of Otago, Dunedin (New Zealand)

[****] We thank the Science Research Council for financial support.

[*****] *Editorial note:* According to IUPAC Rule C-41.2, "dehydro" only denotes the loss of *two* hydrogen atoms when used on its own with a trivial name. If more than two hydrogen atoms are missing, then their exact number should be indicated by the appropriate multiplying prefix in front of "dehydro". The correct name would thus read "tetradehydro ...".

The ^{1}H-NMR parameters of compounds *(8)*, *(9)*, *(11)*, and *(12)* are given in Table 1. The assignments of the H^A and H^B protons in *(8)* and *(9)* follow from the NMR spectra of the corresponding dideuterio derivatives (D instead of H^A), prepared from D_2-3,4-furandicarboxaldehyde [*(4)*, R = CDO instead of CHO][13] and *(6)*. The chemical shift differences for each resonance on passing from the precursors *(8)* and *(11)* to the corresponding macrocycles *(9)* and *(12)* are also given in Table 1. The fact that the "fixed" outer proton

signals in *(9)* and *(12)* have all moved slightly downfield could be due to the weakly diatropic nature of the macrocyclic



rings in these substances. As regards the protons on the *trans* double bonds of *(9)* and *(12)*, it is evident that the H^A resonances have shifted slightly downfield and the H^B resonances upfield. In view of the behavior of related substances[10] we believe *(9)* and *(12)* are probably conformationally mobile[14]. The observed shifts of the H^A and H^B signals would then indicate the predominance of a conformation having H^A external and H^B internal.

The tetradehydrocyclotetradeca[*c*]furans *(9)* and *(12)*, like isobenzofuran *(2)*, are $(4n+2)$ π-electron systems, but appear to be more weakly diatropic[4]. In view of the marked difference in properties between isobenzofuran *(2)* [$(4n+2)$ π-electrons] and cyclobuta[*c*]furan *(1)* [$4n$ π-electrons], it will be of interest to compare the properties of *(9)* and *(12)* with related macrocyclic systems containing $4n$ π-electrons.

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German version: Angew. Chem. 86, 163 (1974)

[1] Unsaturated macrocyclic compounds. Part 103.—Part 102: *N. Darby, K. Yamamoto*, and *F. Sondheimer*, J. Amer. Chem. Soc., in the press.

[2] *K. P. C. Vollhardt* and *R. G. Bergman*, J. Amer. Chem. Soc. *94*, 8950 (1972).

[3] *E. LeGoff* and *R. B. LaCount*, Tetrahedron Lett. *1965*, 2787.

[4] *R. N. Warrener*, J. Amer. Chem. Soc. *93*, 2346 (1971); *D. Wege*, Tetrahedron Lett. *1971*, 2337; *U. E. Wiersum* and *W. J. Mijs*, J. C. S. Chem. Commun. *1972*, 347.

[5] *M. J. Cook* and *E. J. Forbes*, Tetrahedron *24*, 4501 (1968).

[6] *J. A. Elix, M. V. Sargent*, and *F. Sondheimer*, J. Amer. Chem. Soc. *92*, 973 (1970).

[7] *P. J. Beeby* and *F. Sondheimer*, Angew. Chem. *85*, 406 (1973); Angew. Chem. internat. Edit. *12*, 411 (1973).

[8] *P. Schiess* and *H. L. Chia*, Helv. Chim. Acta *53*, 485 (1970); *G. M. Pilling* and *F. Sondheimer*, J. Amer. Chem. Soc. *93*, 1970 (1971).

[9] The ε values are minimum ones, due to the instability of the substance in solution.

[10] *R. T. Weavers* and *F. Sondheimer*, Angew. Chem. *86*, 165 (1974); Angew. Chem. internat. Edit. *13*, 139 (1974); *P. J. Beeby, R. L. Wife*, and *F. Sondheimer*, unpublished experiments.

[11] *E. R. H. Jones* and *B. C. L. Weedon*, J. Chem. Soc. *1946*, 937; *I. M. Heilbron, E. R. H. Jones*, and *M. Julia*, *ibid. 1949*, 1430.

[12] The alternative route, corresponding to the reaction of *(4)* and *(6)*, could not be followed, since the phosphonium salt could not be prepared from *cis*-5-bromo-3-methyl-3-penten-1-yne and triphenylphosphane.

[13] This dideuterio compound was synthesized by reduction of diethyl 3,4-furandicarboxylate with $LiAlD_4$, and subsequent oxidation with MnO_2 and then with $Pb(OAc)_4$ [5].

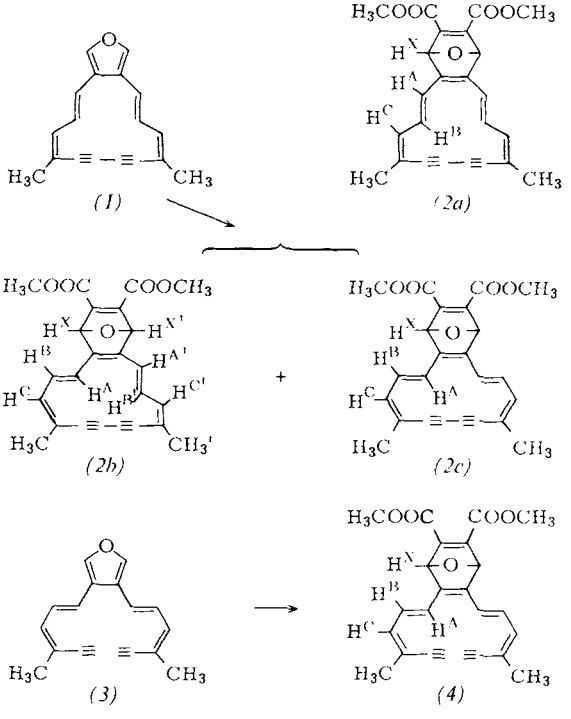
[14] Attempts to prove this through cooling were unsuccessful, since the NMR spectra of *(9)* and *(12)* at *ca.* −70 °C were essentially unchanged.

The Synthesis of 1,3,5,7,9-Cyclotetradecapentaene-11,13-diynes ("1,3-Didehydro[14]annulenes"). The Interconversion between Nonequivalent Conformers of Diatropic Dehydroannulenes[1][***]

By *Rex T. Weavers* and *Franz Sondheimer*[*]

We describe the synthesis of the alkylated "1,3-didehydro[14]annulenes"[****] *(2)* and *(5)*[2], which were required as models for related benzoannelated compounds, described in the following communication[3]. As expected, the ^{1}H-NMR spectra of these $(4n+2)$ π-electron systems showed them to be strongly diatropic. However, an unexpected interconversion between nonequivalent conformers was observed, these being the first diatropic dehydroannulenes to exhibit this phenomenon[4].

7,12-Dimethyl-8,9,10,11-tetradehydrocyclotetradeca[*c*]furan *(1)*[1] was treated in benzene with dimethyl acetylenedicarboxylate (DMAD) for 16 h at room temperature. This dienophile was chosen so as to obtain a single product possessing a potential plane of symmetry. The resulting adduct dimethyl 8,13-dimethyl-9,10,11,12-tetradehydro-1,4-dihydro-1,4-epoxybenzocyclotetradecene-2,3-dicarboxylate *(2)*, a tetraalkylated 1,3-didehydro[14]annulene, formed red-brown crystals[5] [90% yield; *m/e* 388.130 (calcd. 388.131); λ_{max} (ether) *ca.* 275 sh (ε 10600), *ca.* 315 sh (45400), 332 (54400), 435 (8100), 512 (250), 524 (240) *ca.* 560 sh (250) and 573 (280)]. As a model, the rather unstable "open" adduct *(4)* was prepared, in 30% yield, from the terminal diacetylene *(3)*[11] and DMAD.



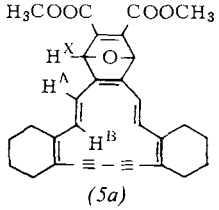
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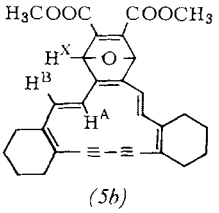
[***] We thank the Science Research Council for financial support.

[****] *Editorial note:* According to IUPAC Rule C-41.2, "dehydro" only denotes the loss of *two* hydrogen atoms when used on its own with a trivial name. If more than two hydrogen atoms are missing, then their exact number should be indicated by the appropriate multiplying prefix in front of "dehydro". The correct name would thus read "tetradehydro ...".

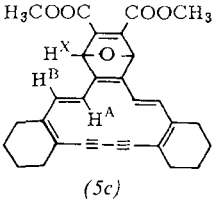
Similarly, reaction of the octahydrodibenzo analog of *(1)*[1] with DMAD led to the adduct dimethyl 11,12,13,14-tetradehydro-1,4,7,8,9,10,15,16,17,18-decahydro-1,4-epoxytribenzo-[*a,e,i*]cyclotetradecen-2,3-dicarboxylate *(5)*, a "hexaalkyl-1,3-didehydro[14]annulene", as orange-red needles[5] [75% yield; *m/e* 468.192 (calcd. 468.194); λ_{max} (ether) 318 (ε 38400), 337 (40400), *ca.* 425 sh (5400), 438 (6100), *ca.* 505 sh (250), *ca.* 520 sh (210), 554 (160), and 567 nm (190)]. The corresponding "open" adduct *(6)* was obtained as orange needles[5] in 35% yield from the corresponding analog of *(3)*[1] and DMAD.



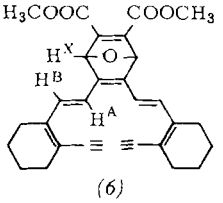
(5a)



(5b)



(5c)



(6)

The ^{1}H-NMR spectra of both the "didehydro[14]annulenes" *(2)* and *(5)* were found to be temperature dependent. The spectrum of *(2)* at −60 °C indicated it to be a *ca.* 7:3 mixture of the unsymmetrical conformer *(2b)* and the symmetrical conformer *(2c)*, these being strongly diatropic. The bands assigned to these conformers are given in Table 1. The fact that there were two high-field doublets corresponding to H^A shows both *(2b)* and *(2c)* to be present. That there was only one high-field double doublet corresponding to H^B (with the same intensity as one of the H^A bands) indicates the absence of conformer *(2a)*. The fact that there were three H^X, three CCH_3 and three OCH_3 resonances confirms the presence of one symmetrical and the unsymmetrical conformer. The individual assignments are based on the integration of the spectrum [which also gives the indicated ratio of *(2b)* and *(2c)*] as well as on double resonance experiments.

Heating the "didehydro[14]annulene" *(2)* above −60 °C results in the coalescence successively of the OCH_3, CCH_3, H^X, H^C, and finally the H^A, H^B signals (approximate coalescence temperatures: −25, −10, 0, +10, and +40 °C, respectively). Above 75 °C, "average" bands due to the H^A, H^B protons appear, the spectrum at 100 °C being given in Table 1. If the conformers *(2b)* and *(2c)* are assumed to be present in the ratio of 7:3, the calculated "average" positions of the H^A and H^B resonances are τ 8.06 and 5.57, respectively, in quite good agreement with the observed values.

In order to obtain quantitative data regarding the diamagnetic ring current in *(2b)* and *(2c)*, the ^{1}H-NMR spectral data of the model *(4)* are also given in Table 1, as well as the chemical shift differences for the various resonances on passing from *(4)* (at 30 °C) to *(2b)* and *(2c)* (at −60 °C). This shows the magnitude of the upfield shift of the inner proton signals and the downfield shift of the outer proton signals.

Table 2. ^{1}H-NMR parameters of *(5)* and *(6)* in $CDCl_3$ at 100 MHz (τ values, TMS internal, *J* in Hz).

	(5) −60 °C	*(5)* 60 °C	*(6)* [b] 30 °C	Δ *(5)*—*(6)* [c]
H^A	10.18 d	6.33 d	3.38 d	+6.80
	1.66 d			−1.72
J	15.5	16	15.5	
	16			
H^B	1.76 d	5.44 d	2.73 d	−0.97
	11.10 d			+8.37
J	15.5	16	15.5	
	16			
H^X	2.88 s	3.38 s	4.00 s	−1.12
	3.65 s [a]			−0.35
Allylic-H	6.6 m	6.8 m	7.7 m	−1.1
Nonallylic-H	8.0 m	8.0 m	8.3 m	−0.3
OCH_3	6.14 s	6.23 s	6.16 s	—
	6.18 s			

[a] In addition, small singlets at τ = 2.50 and 3.13.
[b] In addition, *(6)* shows a singlet at τ = 6.58 (≡CH).
[c] Referred to values for *(5)* at −60 °C.

The ^{1}H-NMR parameters of the "didehydro[14]annulene" *(5)* at −60 °C are given in Table 2. The assignments of the H^A and H^B protons follow from the NMR spectrum of the dideuterio derivative *(5)* (D instead of H^A), prepared from the corresponding furan derivative[1] and DMAD. The relative intensities of the four olefinic resonances were approximately

Table 1. ^{1}H-NMR parameters of *(2)* and *(4)* in $CDCl_3$ at 100 MHz (τ values, TMS internal, *J* in Hz).

	(2b) [a] −60 °C	*(2c)* [a] −60 °C	*(2)* [c] 100 °C	*(4)* [d] 30 °C	Δ *(2b)*—*(4)*	Δ *(2c)*—*(4)*
H^A	11.49 d	12.12 d	8.03 br	3.45 d	+ 8.04	+8.67
J	14	15		15		
H^B	1.63 dd	1.22 dd	5.20 br	3.05 dd	− 1.42	−1.83
J	14,8.5	15,9		15,11		
H^C	[b]	1.79 d	1.61 d	3.59 d	—	−1.80
J		9	10	11		
$H^{A'}$	1.14 d	—	—	3.45d	− 2.31	—
J	16			15		
$H^{B'}$	13.23 dd	—	—	3.05dd	+10.18	—
J	16,12			15, 11		
$H^{C'}$	1.06 d	—	—	3.59d	− 2.53	—
J	12			11		
H^X	2.98 s	2.68 s	3.20 s	4.04 s	− 1.06	−1.36
$H^{X'}$	3.48 s	—	—	4.04 s	− 0.56	—
CCH_3	6.97 s	7.02 s	7.03 s	8.00 s	− 1.03	−0.98
CCH'_3	6.90 s	—	—	8.00 s	− 1.10	—

[a] In addition, *(2b)* and *(2c)* at −60 °C show singlets at τ = 6.16, 6.22, and 6.25 (OCH_3).
[b] The chemical shift of this proton could not be determined.
[c] In addition, *(2)* at 100 °C shows a singlet at τ = 6.25 (OCH_3).
[d] In addition, *(4)* shows singlets at τ = 6.17 (OCH_3) and 6.57 (≡CH).

equal. This shows that *(5)* exists mainly as the unsymmetrical conformer *(5b)* or mainly as an approximately equal mixture of the two symmetrical conformers *(5a)* and *(5c)*. However, the presence of two small additional H^X bands (Table 2, footnote [a]) indicates that all three conformers are present to some extent.

Heating *(5)* above $-60\,^{\circ}C$ again results in the coalescence of the various ^{1}H-NMR signals, the approximate coalescence temperature being $-25\,^{\circ}C$ for H^X and $0\,^{\circ}C$ for H^A, H^B. Above $25\,^{\circ}C$, "average" bands due to the H^A, H^B protons appear, and the spectrum at $60\,^{\circ}C$ is given in Table 2. The spectral data of the model *(6)* are also given in Table 2, as well as the chemical shift differences on passing from *(6)* (at $30\,^{\circ}C$) to *(5)* (at $-60\,^{\circ}C$). The differences indicate the upfield shift of the inner proton resonances in *(5)* and the downfield shift of the outer proton resonances.

It is apparent that "didehydro[14]annulene" *(5)* is appreciably less diatropic than *(2)*, as indicated by comparison of their ^{1}H-NMR spectra with those of the corresponding models *(6)* and *(4)* (Tables 1 and 2). Presumably, this effect is due to steric interaction in *(5)*, reducing its planarity. The fact that *(5)* is more "mobile" than *(2)*, as shown by comparison of the coalescence temperatures, is probably due to the same factor.

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[1] Unsaturated macrocyclic compounds. Part 104.—Part 103: *P. J. Beeby, R. T. Weavers*, and *F. Sondheimer*, Angew. Chem. *86*, 163 (1974); Angew. Chem. internat. Edit. *13*, 138 (1974).

[2] For the synthesis of other dehydro[14]annulenes, see *F. Sondheimer*, Proc. Roy. Soc. *A 297*, 173 (1967); Accounts Chem. Res. *5*, 81 (1972), and references given there; *K. Fukui, T. Nomoto, S. Nakatsuji*, and *M. Nakagawa*, Tetrahedron Lett. *1972*, 3157.

[3] *R. T. Weavers* and *F. Sondheimer*, Angew. Chem. *86*, 167 (1974); Angew. Chem. internat. Edit. *13*, 141 (1974).

[4] For examples of this phenomenon in paratropic dehydro[16]annulenes, see *I. C. Calder, Y. Gaoni, P. J. Garratt*, and *F. Sondheimer*, J. Amer. Chem. Soc. *90*, 4954 (1968).

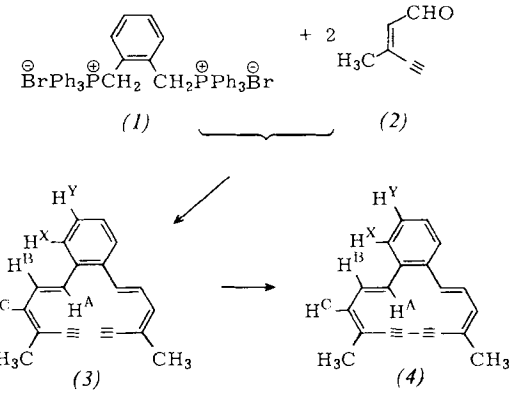
[5] The substance decomposed on attempted melting point determination.

The Synthesis of Tetradehydrobenzocyclotetradecenes ("Benzodidehydro[14]annulenes"). The Effect of Benzoannelation on the Diamagnetic Ring Current of Macrocyclic $(4n+2)$ π-Electron Systems[1][***]

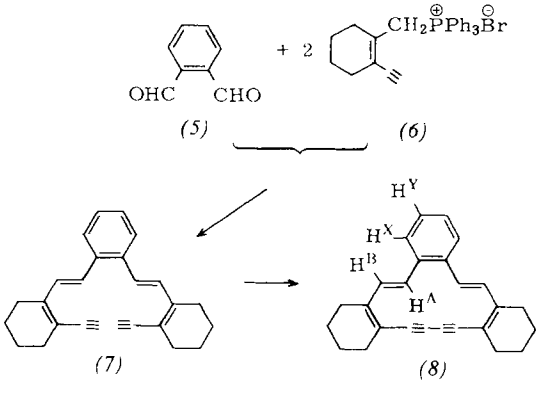
By *Rex T. Weavers* and *Franz Sondheimer*[*]

The fact that "aromatic" macrocyclic and bridged macrocyclic $(4n+2)$ π-electron systems show a diamagnetic ring current, as determined by ^{1}H-NMR spectrometry, is now well established[2]. It was of considerable interest to investigate the effect on the ring current produced by benzoannelation of these systems. There are indications that it suppresses the ring current[3], although little quantitative data is available. We now describe the synthesis of the tetradehydrobenzocyclotetradecenes ("benzodidehydro[14]annulenes")[****] *(4)* and *(8)*, and show that annelation of the benzene ring reduces, but does not completely suppress, the diamagnetic ring current of the 14-membered ring.

Wittig reaction of *o*-xylylenebis(triphenylphosphonium bromide) *(1)*[4] and two molar equivalents of *cis*-3-methyl-2-penten-4-ynal *(2)*[5] in dimethylformamide with ethanolic lithium ethoxide at $80\,^{\circ}C$ led to a stereoisomeric mixture, which on chromatography on alumina (Woelm, neutral) gave the di-*trans* compound *(3)* in 14% yield as light yellow needles, m.p. 128—130 °C (decomp.) [*m/e* 258.142 (calcd. 258.141), λ_{max} (ether) 293 (ε 25800) and 331 nm (29900)]. Oxidative coupling of *(3)* with cupric acetate in pyridine at $60\,^{\circ}C$ under relatively dilute conditions then furnished 5% of 8,13-dimethyl-9,10,11,12-tetradehydrobenzocyclotetradecene *(4)* as pale orange needles, m.p. 174—175 °C [*m/e* 256.125 (calcd. 256.125): λ_{max} (ether) 263 (ε 10500), 276 (13100), 318 (54000), *ca.* 370 sh (6000), 393 sh (4900), and *ca.* 410 sh nm (3000)].



Wittig reaction of phthaldialdehyde *(5)* and two molar equivalents of the phosphonium salt *(6)*[6] essentially under the previously indicated conditions again gave a stereoisomeric mixture. Chromatography on alumina yielded *ca.* 25% of the *cis,trans* isomer corresponding to *(7)*, followed by *ca.* 35% of an inseparable mixture of the di-*trans* isomer *(7)* and the corresponding di-*cis* isomer (assignments based on ^{1}H-NMR spectrometry). Oxidative coupling of this mixture essentially as before, and separation by multiple-run preparative layer chromatography on Kieselgel, then led to 11% of di-*trans* 11,12,13,14-tetradehydro-7,8,9,10,15,16,17,18-octahydrotribenzo[*a,e,i*]cyclotetradecene *(8)* as yellow needles, m.p. 160—161.5 °C [*m/e* 336.188 (calcd. 336.188); λ_{max} (ether) 264 (ε 10600), *ca.* 280 sh (13900), 313 (34900), and 368 sh nm (5600)][7].



The ^{1}H-NMR parameters of *(3)* and *(4)* are given in Table 1. In the assignment of the benzenoid protons, the assumption has been made that H^X is more affected than H^Y by the

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[***] We thank the Science Research Council for financial support.

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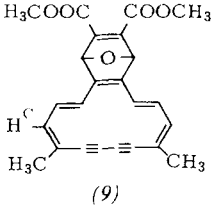
unsaturated substituents. Comparison of the spectra of these substances (Table 1) shows that *(4)* is moderately diatropic, as evidenced by the magnitude of the downfield shift of the H^C and CH_3 resonances. The fact that the H^A signal in *(4)* has moved upfield as compared to that in *(3)*, and the H^B signal downfield, points to a conformation having H^A internal and H^B external. However, in view of the fluxional behavior of the related diatropic compound *(9)*[1], we believe that *(4)* is probably also conformationally mobile[8], the indicated conformation predominating. The mobility is substantiated by the fact that the downfield shift of the resonance due to H^C, which is fixed, is considerably greater than that of H^B.

Table 1. ^{1}H-NMR parameters of *(3)* and *(4)* in $CDCl_3$ at 100 MHz (τ values, TMS internal, *J* in Hz).

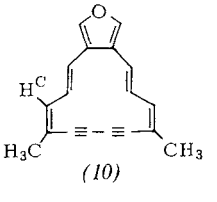
	(3) [a]	*(4)*	Δ *(4)*—*(3)*
H^A	3.12 d	5.01 d	+1.89
J	15.5	16	
H^B	2.83 dd	2.56 dd	−0.27
J	15.5,10	16,7.5	
H^C	3.51 d	2.92 d	−0.59
J	10	7.5	
CH_3	8.01 s	7.64 s	−0.37
H^X	2.47 m	1.75 m	−0.72
H^Y	2.78 m	2.49 m	−0.29

[a] In addition, *(3)* shows a singlet at τ = 6.68 (≡CH).

Interestingly, the benzenoid proton (H^X, H^Y) resonances in the ^{1}H-NMR spectrum of *(4)* have shifted appreciably downfield as compared with those of *(3)*[9] (Table 1), this effect, as expected, being greater for H^X than H^Y. This is a reversal of the behavior of the benzene protons of benzocyclobutene derivatives, in which the $4n$ π-electron cyclobutadiene ring causes the benzenoid proton resonances to shift to higher field[10].



(9)



(10)

The ^{1}H-NMR spectrum of *(8)* ($CDCl_3$, 100 MHz) consisted of 2H multiplets at τ = 2.01 (H^X) and 2.58 (H^Y), 2H doublets at 3.06 and 4.02 (H^A, H^B), as well as 8H multiplets at 7.4 (allylic H) and 8.2 (nonallylic H). This again is presumably a fluxional molecule. The ^{1}H-NMR spectrum of the acyclic analog *(7)* was not available, but the diatropic nature of *(8)* is indicated by the downfield shift of the allylic proton resonances (*ca.* −0.3 ppm) as compared with the normal value, as well as by the downfield shift of the benzenoid proton resonances H^X (−0.46 ppm) and H^Y (−0.20 ppm) relative to those of the model *(3)*.

Comparison of the ^{1}H-NMR spectral data shows the relative magnitude of the ring currents in the "didehydro[14]annulenes" *(4)*, *(9)*[1] and *(10)*[11]. The macrocyclic ring in the tetraalkyl compound *(9)* is strongly diatropic, in the benzoannelated compound *(4)* it is moderately diatropic, and in the fused furan *(10)* it is at most weakly diatropic. In view of the conformational mobility of these substances [*(9)*, *(4)*, *(10)*], this is most easily seen by the downfield shifts, as compared with the respective models, of the H^C bands (*ca.* −2.0, −0.6, and −0.3 ppm, respectively) and of the CH_3 bands (*ca.* −1.0, −0.4, and −0.1 ppm, respectively). The corresponding cyclohexene-fused compounds [cf. *(5)* in [1], *(8)* in this communication, and *(9)* in [11]] follow the same order, as shown by the downfield shifts of the allylic proton resonances (*ca.* −1.1, −0.3, and −0.1 ppm, respectively).

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[1] Unsaturated macrocyclic compounds. Part 105.—Part 104: *R. T. Weavers* and *F. Sondheimer*, Angew. Chem. *86*, 163 (1974); Angew. Chem. internat. Edit. *13*, 138 (1974).

[2] For references, see *R. C. Haddon, V. R. Haddon*, and *L. M. Jackman*, Fortschr. Chem. Forsch. *16*, 103 (1971); *F. Sondheimer*, Accounts Chem. Res. *5*, 81 (1972).

[3] See *K. Endo, Y. Sakata*, and *S. Misumi*, Tetrahedron Lett. *1970*, 2557; *H. Günther, H. Schmickler, H. Königshofen, K. Recker*, and *E. Vogel*, Angew. Chem. *85*, 261 (1973); Angew. Chem. internat. Edit. *12*, 243 (1973).

[4] *C. E. Griffin, K. R. Martin*, and *B. E. Douglas*, J. Org. Chem. *27*, 1627 (1962); *C. E. Griffin* and *J. A. Peters, ibid. 28*, 1715 (1963).

[5] *E. R. H. Jones* and *B. C. L. Weedon*, J. Chem. Soc. *1946*, 937; *I. M. Heilbron, E. R. H. Jones*, and *M. Julia, ibid. 1949*, 1430.

[6] *P. J. Beeby* and *F. Sondheimer*, Angew. Chem. *85*, 406 (1973); Angew. Chem. internat. Edit. *12*, 411 (1973).

[7] Substance *(8)* was followed by 6% of the corresponding di-*cis* isomer, yellow crystals which decomposed on attempted melting point determination [*m/e* 336.189 (calcd. 336.188); λ_{max} (ether) 281 (ε 16900) and 356 nm sh (4400)]. The ^{1}H-NMR spectrum of this isomer [CCl_4, 100 MHz: τ = 2.88 (2H/m, benzenoid), 3.08 (2H/m, benzenoid), 3.68 (2H/d, *J* = 12.5 Hz, olefinic), 4.32 (2H/broad d, *J* = 12.5 Hz, olefinic), 7.65 (4H/m, allylic), 7.95 (4H/m, allylic), and 8.3 (8H/m, nonallylic)] showed it to be atropic, and it is presumably a nonplanar molecule.

[8] The ^{1}H-NMR spectrum of *(4)* was essentially temperature independent in the range −80 to 60 °C.

[9] See *D. Cremer* and *H. Günther*, Liebigs Ann. Chem. *763*, 87 (1972).

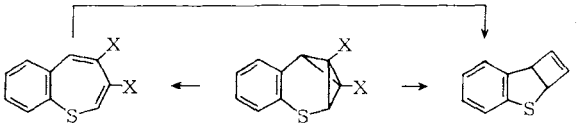
[10] See, *inter al.*, *H. P. Figeys*, Chem. Commun. *1967*, 495; *P. J. Garratt* and *K. P. C. Vollhardt*, Angew. Chem. *83*, 111 (1971); Angew. Chem. internat. Edit. *10*, 125 (1971); *P. J. Garratt* and *K. P. C. Vollhardt*, J. Amer. Chem. Soc. *94*, 7087 (1972).

[11] *P. J. Beeby, R. T. Weavers*, and *F. Sondheimer*, Angew. Chem. *86*, 165 (1974); Angew. Chem. internat. Edit. *13*, 139 (1974).

Synthesis and Reactions of 1-Benzothiepin

By *Ichiro Murata, Toshio Tatsuoka*, and *Yoshikazu Sugihara*[*]

Although several substituted derivatives have been prepared, the parent 1-benzothiepin *(1)* has never been synthesized because of its thermal instability[1-3]. *Traynelis* and *Yoshikawa* have recently reported the synthesis of *(1)* from 2,3-dihydro-2-chloro-1-benzothiepin and $KOC(CH_3)_3$[4]; however, none of its properties have so far been reported.



(1), X = H *(1a)*, X = D *(2)*, X = H *(2a)*, X = D *(3)*

In the course of other investigations[5] we had been able to isolate 6-thiatetracyclo[5.4.0.0^{2,4}.0^{3,5}]undeca-1(7),8,10-triene *(2)*—a valence isomer of *(1)*—in moderate yields[5d, 5e]. We describe here the novel synthesis of 1-benzothiepin *(1)* by Rh^I-catalyzed isomerization of *(2)*[6].

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Treatment of *(2)* with 7.8 mole-% of dicarbonyl-2,4-pentanedionatorhodium(I) (16 h at 0 °C in chloroform) leads to 57% of *(1)* (pale yellow needles, m. p. 23.5—24.5 °C)[7], which was purified by low-temperature column chromatography on alumina (deactivated with 5% water) at −20 °C. All manipulations during work-up have to be carried out below −10 °C in order to avoid contamination with naphthalene. The structure of *(1)* was established by a combination of elemental analysis[7], UV and NMR spectroscopy: The UV spectrum of *(1)* [λ_{max} (cyclohexane) = 217 nm (log ε = 4.07), 256 (4.07), 295 sh (2.96), 345 nm (broad, weak) (2.55)] is closely similar to those reported for the substituted 1-benzothiepins[2a]. The NMR spectrum [100 MHz ($CDCl_3$), TMS int., −20 °C: δ = 5.90 (2-H), 6.34—6.56 (3-H, 4-H), and 7.09 (5-H), 7.15—7.5 (aromat. H)] was assigned on the basis of relative chemical shifts, shielding of 2-H being larger than that of 3-H[2a]. [3,4-D_2]-1-Benzothiepin *(1a)*, obtained from *(2a)*[5e], exhibited in addition to the multiplet of the four aromatic protons (δ = 7.05—7.4), two equally intense broad singlets (1 H) at δ = 5.85 and 7.00.

Chemical proof of the structure of *(1)* was gained by catalytic hydrogenation in ethanol over a large amount of palladium-charcoal. This reduction yielded 2,3,4,5-tetrahydro-1-benzothiepin, which was identical with an authentic sample[8]. Warming of *(1)* in carbon tetrachloride leads to formation of naphthalene and sulfur with a (NMR spectroscopically determined) half-life of transformation of 80 min at 40 °C.

Treatment of *(1)* with *m*-chloroperbenzoic acid in CH_2Cl_2 at −20 °C afforded 1-benzothiepin-1,1-dioxide in 87% yield, m. p. 138—139 °C ([8]: 140—141 °C). NMR, δ = 6.6—7.1 (m, 3 H), 7.4—7.9 (m, 4 H) and 8.1—8.4 (m, 1 H). Irradiation of *(1)* in THF (450-W high-pressure mercury arc lamp, pyrex filter, 4 h at 0 °C) yielded the known valence isomer *(3)*[5e] along with a small amount of naphthalene. *(3)* is also formed from *(2)* by irradiation or by $AgClO_4$ catalysis[5e].

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[1] *L. A. Paquette* in *J. P. Snyder*: Nonbenzenoid Aromatics. Academic Press, New York 1969, Vol. 1, Ch. 5.

[2] a) *H. Hofmann*, *B. Meyer*, and *P. Hofmann*, Angew. Chem. *84*, 477 (1972); Angew. Chem. internat. Edit. *11*, 423 (1972); b) *H. Hofmann* and *H. Westernacher*, Chem. Ber. *102*, 205 (1969); c) *D. N. Reinhoudt* and *C. G. Kouwenhoven*, J. C. S. Chem. Comm. *1972*, 1232; d) *V. J. Traynelis* in *A. Weissberger* and *E. C. Taylor*: The Chemistry of Heterocyclic Compounds. Wiley-Interscience, New York 1972, Vol. 26, Ch. 11.

[3] *V. J. Traynelis* and *J. R. Livingston, Jr.*, J. Org. Chem. *29*, 1092 (1964).

[4] *V. J. Traynelis* and *Y. Yoshikawa*, Abstracts, 164th National Meeting of the American Chemical Society, New York, N. Y., 1972, No. ORGN-56.

[5] a) *I. Murata* and *K. Nakasuji*, Tetrahedron Lett. *1973*, 43; b) *ibid. 1973*, 1591; c) *I. Murata*, *K. Nakasuji*, and *H. Kume*, *ibid. 1973*, 3401, 3405; d) *I. Murata*, *T. Tatsuoka*, and *Y. Sugihara*, *ibid. 1973*, 4261; e) *ibid.*, in the press.

[6] For a review see: *D. J. Cardin*, *B. Cetinskaya*, *M. J. Doyle*, and *M. F. Lappert*, Chem. Soc. Rev. *2*, 99 (1973).

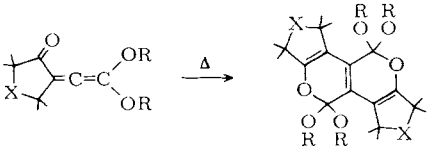
[7] Satisfactory C, H analytical values were obtained for *(1)*.

[8] *V. J. Traynelis* and *R. F. Love*, J. Org. Chem. *26*, 2728 (1961); *W. E. Truce* and *J. P. Milionis*, J. Amer. Chem. Soc. *74*, 974 (1952).

Dimerization of "Push-Pull" Substituted Allenes

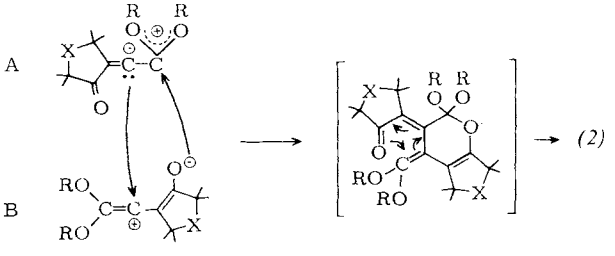
By *Rolf W. Saalfrank*[*]

The dimerization of allenes in a [2+2]cycloaddition[1] leading to 1,2-bis(methylene)cyclobutane derivatives is well known. Far less attention has been paid to allene dimerizations proceeding with substituent participation, such as the formation of dehydroacetic acid from allenecarboxylic acid[2] or the dimerization of triphenylchloroallenes to give derivatives of rubrene[3]. The present communication reports the dimerization of the diethoxyvinylidene-tetrahydrofuranones *(1a)* and -cyclopentanones *(1b)* affording the tetracyclic compounds *(2a)* and *(2b)* respectively, which resembles the dimerization of triphenylchloroallenes mentioned above.



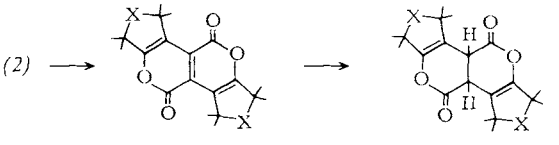
(1a), X = O
(1b), X = CH_2
R = C_2H_5
(2a), X = O
(2b), X = CH_2

The allenes *(1)* can be described in terms of the resonance structures A and B. It is assumed that 1,4-dipolar cycloaddition of the α,β-unsaturated keto system of one allene molecule to the ketene acetalic double bond of another leads initially to the cisoid 2,2-diethoxypyran intermediate *(3)*. This intermediate then undergoes an electrocyclic reaction analogous to hexatriene-cyclohexadiene isomerization to give the dimer *(2)* whose structure follows unequivocally from the spectroscopic data listed in Table 1.



(1) *(3)*
X = O, CH_2;
R = C_2H_5

In boiling glacial acetic acid the diethoxypyrans *(2)* are converted almost quantitatively into the fused α-pyrones *(4)*.



(4a), X = O
(4b), X = CH_2
(5a), X = O
(5b), X = CH_2

These strongly fluorescing substances exhibit powerful emission on excitation of their saturated methylene chloride solutions by a nitrogen laser. Owing to their remarkable stability they are particularly suited for use as laser dyes. The following spectroscopic data not listed in Table 1 were obtained for compounds *(4a)* and *(4b)*: UV spectrum (C_2H_5OH): λ_{max} = 410 nm (ε = 10 500) and 420 nm (12100) respectively; dye

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Table 1. Data of the compounds *(2a)*, *(2b)*, *(4a)*, *(4b)*, *(5a)*, and *(5b)* [5].

Cpd.	Yield [%]	M.p. [°C]	IR (KBr) [cm^{-1}]	^{1}H-NMR (60 MHz, τ values, TMS internal, in $CDCl_3$)
(2a)	48 [a]	140	1634	8.91 (12H, t); 8.55 (12H, s); 8.25 (12H, s); 6.33 (8H, q) [c]
(2b)	45 [a]	144	1621	8.85 (12H, t); 8.84 (12H, s); 8.70 (12H, s); 8.35 (4H, s); 6.42 (8H, q)
(4a)	96	291 [b]	1730, 1608	8.55 (12H, s); 8.34 (12H, s)
(4b)	93	252 [b]	1727, 1590	8.73 (12H, s); 8.55 (12H, s); 8.09 (4H, s)
(5a)	65	215	1773, 1704	8.81 (12H, s); 8.71 (6H, s); 8.68 (6H, s); 7.06 (2H, s) [c]
(5b)	63	179	1764, 1695	8.85 (24H, s); 8.25 (4H, s); 6.54 (2H, s)

[a] Based on the amount of 2,2-diethoxyvinylphosphonium salt.
[b] Slow sublimation above about 200°C.
[c] In C_6D_6.

laser emission spectrum (CH_2Cl_2): λ_{max} laser ≈ 485 and 510 nm, and 495 and 515 nm respectively[6].

Reduction of the α-pyrones *(4)* with zinc in glacial acetic acid gives the fused lactones *(5)* in good yields[7].

4,4,9,9-Tetraethoxy-1,1,3,3,6,6,8,8-octamethyl-1,3,4,6,8,9-hexahydro-2,5,7,10-tetraoxaindeno[5,4-e]indene (2a) and -1,2,3,4,6,7,8,9-octahydro-5,10-dioxaindeno[5,4-e]indene (2b)

A benzene solution of 2,2,5,5-tetramethyltetrahydrofuran-3,4-dione (5.5 g, 35 mmol) or 3,3,5,5-tetramethyl-1,2-cyclopentanedione (5.4 g, 35 mmol) is rapidly added dropwise to a stirred, cooled benzene solution of 2,2-diethoxyvinylidenetriphenylphosphorane[1a] prepared from 2,2-diethoxyvinyltriphenylphosphonium tetrafluoroborate (18.0 g, 40 mmol). The solvent is drawn off at room temperature, the resinous residue extracted several times with light petroleum, and triphenylphosphane oxide is filtered off. After removal of the light petroleum and subsequent bulb distillation (*ca.* 110°C/0.5 torr), 2-(2,2-diethoxyvinylidene)-3,3,5,5-tetramethylcyclopentanone *(1b)* (5.1 g, 20 mmol) is obtained which undergoes almost complete dimerization to *(2b)* on prolonged heating at about 140—160°C. 4-(2,2-Diethoxyvinylidene)-2,2,5,5-tetramethyltetrahydrofuran-3-one *(1a)* cannot be isolated under the above experimental conditions and *(2a)* is obtained directly on removal of the light petroleum. The dimers *(2)* can be recrystallized from ether.

1,1,3,3,6,6,8,8-Octamethyl-1,3,6,8-tetrahydro-2,5,7,10-tetraoxaindeno[5,4-e]indene-4,9-dione (4a) and -1,2,3,6,7,8-hexahydro-5,10-dioxaindeno[5,4-e]indene-4,9-dione (4b)

(2a) or *(2b)* (5 mmol) is refluxed in glacial acetic acid (20 ml) for 30 min. After cooling and filtration, the greenish yellow, strongly fluorescing crystals of *(4a)* or *(4b)* are washed with methanol.

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[1] a) *H. J. Bestmann, R. W. Saalfrank,* and *J. P. Snyder,* Chem. Ber. *106,* 2601 (1973); b) *O. J. Muscio Jr.* and *T. L. Jacobs,* Tetrahedron Lett. *1969,* 2867; c) *T. L. Jacobs* and *O. J. Muscio Jr., ibid. 1970,* 4829; d) *E. V. Dehmlow* and *G. C. Ezimora, ibid. 1972,* 1265.

[2] *G. Eglinton, E. R. H. Jones, G. H. Mansfield,* and *M. C. Whiting,* J. Chem. Soc. *1954,* 3197.

[3] *P. D. Landor* and *S. R. Landor,* J. Chem. Soc. *1963,* 2707.

[4] *R. W. Saalfrank,* Tetrahedron Lett. *1973,* 3985.

[5] All compounds gave correct values on C,H analysis. The expected molecular peak was observed in the mass spectra.

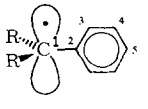
[6] I am grateful to Prof. Dr. *F. P. Schäfer,* Göttingen, for recording the dye laser emission spectrum. See also *D. Basting, F. P. Schäfer,* and *B. Steyer,* Appl. Phys. *3,* 81 (1974).

[7] Determination of the stereochemistry of the lactones *(5)* by X-ray crystal structure analysis is still in progress.

ESR Spectrum of a Perpendicular Benzyl Radical[1]

By *Kurt Schreiner* and *Armin Berndt*[*]

In the same way as the *planar* benzyl radical constitutes a textbook example for π-π delocalization or conjugation, the perpendicular benzyl radical *(1a)* represents a prototype for π-σ delocalization or hyperconjugation, whose significance in chemistry has recently received increasing recognition[2]. INDO calculations[3,4] on *(1a)* predict ESR coupling constants of considerable magnitude for the *ortho* C atoms (17.05 G), *ortho* H atoms (1.97 G), and *meta* H atoms (2.78 G) which arise almost exclusively from π-σ delocalization since the minimal π spin densities at the ring C atoms would lead only to coupling constants of 0.5, 0.3, and 0.2 G by spin polarization.



(1a), R = H
(1b), R = $C(CH_3)_3$

Experimental checks of the INDO results have hitherto been limited to model radicals[4-6] having relatively small spin densities at the exocyclic π center and angles of twist of only about 60°.

The 1,1-di-*tert*-butylbenzyl radical *(1b)* represents the first benzyl radical twisted through 90°. We prepared it by reaction of the oxalic diester[7] of 1,1-di-*tert*-butylbenzyl alcohol with potassium/sodium alloy in benzene. Since *(1b)* is stable for several days at room temperature under the conditions of its preparation, it can be generated in concentrations high enough to determine coupling constants of ^{13}C in natural isotopic abundance. These coupling constants together with the *g* factor of 2.0024 provide proof of the structure and the stereochemistry of the radical *(1b)*.

The following coupling constants can be deduced from the ESR spectrum shown in Figure 1; $a^H = 0.47$ G for 18 equivalent protons (2 tBu), $a^H = 0.31$ G (1 H, *i. e. para* proton), and $a^H = 0.82$ and $a^H = 0.91$ G for two sets of two equivalent protons (*ortho* and *meta*). An ESR spectrum recorded at higher concentration and amplification reveals ^{13}C coupling constants of 45 (1 C), 18.2 (2 C), and 11.7 G (7 C). We assign the largest constant to C^1 since it shows excellent agreement with $a^C = 45.2$ G[8] of the central C atom of the *tert*-butyl radical. $a^C = 18.2$ G (2 C) lies in the range expected for the *ortho* C atoms of a highly twisted benzyl radical from the known relationship $a^C = 19\ \rho_C \cos^2\theta$[5]. The assignment of $a^C = 11.7$ G to the six C atoms of the methyl groups of the *tert*-butyl substituents follows from a comparison with the ^{13}C coupling constants

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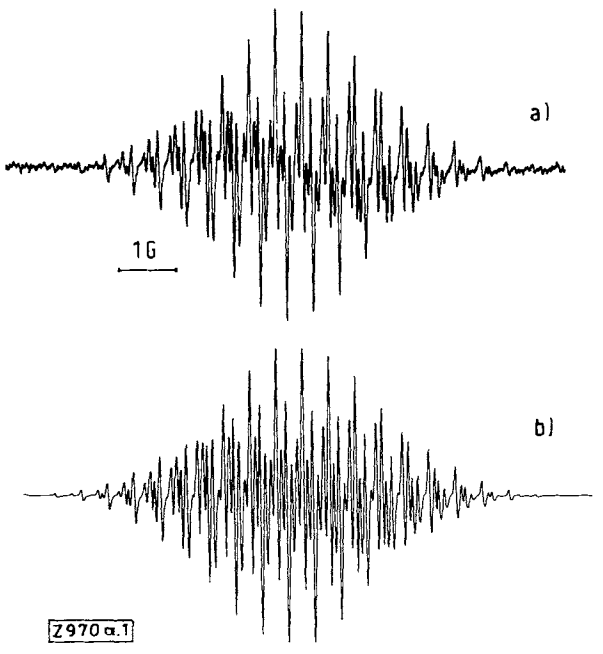


Fig. 1. a) ESR spectrum of the 1,1-di-*tert*-butylbenzyl radical *(1b)* in benzene at 25 °C; b) computer simulation with the coupling constants given in the text, line width 0.03 G.

of the 1,1-di-*tert*-butylmethyl radical (11.7 G for 6 C[9]). The remaining coupling constant of 11.7 G for one C atom is assigned to C^2 since a contribution of *ca.* 12 G is to be expected in this position due to spin polarization (cf. $a^C = 12.35$ G for the methyl C atoms of the *tert*-butyl radical[8]).

Since $a^C_{C^1}$ and $a^C_{C(CH_3)_3}$ for *(1b)* are in complete accord with the corresponding data for the *tert*-butyl and the 1,1-di-*tert*-butylmethyl radical respectively, for which π-π delocalization is precluded, the angle of twist in *(1b)* must be 90° or almost 90°. Supporting evidence comes from the very small coupling constant of the *para* proton (0.31 G as against 6.14 G in the planar benzyl radical[10]) and the very large coupling constant of the *ortho* C atoms (18.2 G) which are both in good agreement with the values calculated for a benzyl radical twisted through 90° (0.23 and 17.05 G).

The contribution from π-σ delocalization in a^H_o and a^H_m found for *(1b)* (0.82 and 0.91 G) is thus considerably smaller than that predicted by INDO calculations (1.97 and 2.78 G) and found experimentally for a^H_m of model radicals[4-6].

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[1] Hyperconjugation in Twisted π-Radicals, Part 5. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 4: *K. Schreiner, A. Berndt,* and *F. Bär*, Mol. Phys. *26*, 929 (1973).

[2] *H. Schmidt* and *A. Schweig*, Angew. Chem. *85*, 299 (1973); Angew. Chem. internat. Edit. *12*, 307 (1973); and further literature cited therein.

[3] *J. A. Pople* and *D. L. Beveridge*, J. Chem. Phys. *49*, 4725 (1968).

[4] *A. Calder, A. R. Forrester, J. W. Emsley, G. R. Luckhurst,* and *R. A. Storey*, Mol. Phys. *18*, 481 (1970); *W. J. van den Hoek, B. A. C. Rousseeuw, J. Smidt, W. G. B. Hysmans,* and *W. J. Mijs*, Chem. Phys. Lett. *13*, 429 (1972).

[5] *G. R. Luckhurst* and *J. N. Ockwell*, Tetrahedron Lett. *1968*, 4123; *A. Berndt, ibid. 1968*, 5439.

[6] *R. Biehl, K. P. Dinse, K. Möbius, M. Plato, H. Kurreck,* and *W. Mennenga*, Tetrahedron *29*, 363 (1973); *P. Ashworth* and *W. T. Dixon*, J. C. S. Perkin *II 1973*, 1533.

[7] The chlorocarbonic ester can be used in place of the oxalic diester. Production of *(1b)* from the oxalate corresponds to the assumed formation of benzyl radicals on electrolytic reduction of dibenzyl oxalate: *J. Voss*, Tetrahedron *27*, 3753 (1971).

[8] *H. Paul* and *H. Fischer*, Helv. Chim. Acta *56*, 1575 (1973).

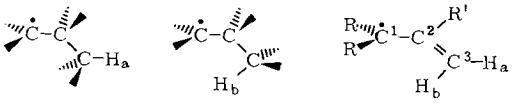
[9] *G. D. Mendenhall* and *K. U. Ingold*, J. Amer. Chem. Soc. *95*, 3422 (1973).

[10] *A. Carrington* and *I. C. P. Smith*, Mol. Phys. *9*, 137 (1965).

Homohyperconjugation in a Perpendicular Allyl Radical[1]

By *Henning Regenstein* and *Armin Berndt*[*]

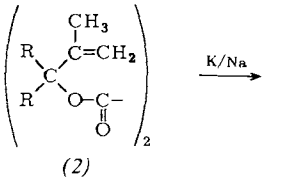
The conformations A and B of the *n*-propyl radical, for which quantum mechanical approximation calculations are available[5-7], represent prototypes for the π-σ delocalization termed *homohyperconjugation*[3] established experimentally for numerous radicals derived from rigid bicyclic systems[3,4]. The "W" or "anti-W" arrangement of π- and σ orbitals required for this π-σ interaction also occurs in extensively twisted π radicals[2]. The perpendicular allyl radical *(1a)*, which has the two relevant protons H_a and H_b of A and B in a similar geometrical arrangement, can be regarded as a prototype of such systems.



A B

(1a), R = R' = H
(1b), R = $C(CH_3)_3$, R' = CH_3

We have now prepared the first stable allyl radical devoid of π-π delocalization, the 1,1-di-*tert*-butyl-2-methylallyl radical *(1b)*, by reaction of the oxalic diester *(2)* with potassium/sodium alloy[8]. Compound *(2)* is obtained by reaction of di-*tert*-butyl ketone with 2-lithio-2-methylpropene and subsequent treatment with oxalyl chloride [*(2)*: m.p. 115 °C; NMR (in CCl_4, δ relative to TMS): singlets at 1.26 (18H), 1.92 (3H), 4.84 (1H), and 5.30 ppm (1H)].



(2)

(1b)
R = $C(CH_3)_3$

The ESR spectrum (Fig. 1) of the radical *(1b)*, which is stable for several days at room temperature, can be simulated with the values $a^H = 0.45$ (18H, 2tBu), $a^H = 0.71$ (3H, CH_3), $a^H = 3.40$ (1H), and $a^H = 0.96$ G (1H). Together with the *g* factor of 2.0025 these coupling constants prove the structure of *(1b)*. Its stereochemistry follows from the ^{13}C coupling constants of 46 (1C), 18 (2C), and 12 G (9C), which could be determined when the amplification of the spectrum was increased. Since these constants are in very good agreement with the corresponding constants of the 1,1-di-*tert*-butylbenzyl radical[9] which is known to be twisted through 90°, *(1b)* must likewise be twisted through 90° or almost 90°. In this conformation the bulky *tert*-butyl groups are located at the farthest possible distance from the methyl groups on C^2.

The orthogonality of the p orbitals on C^1 and C^2 ensures that the π-spin density at C^3 is virtually zero. Coupling con-

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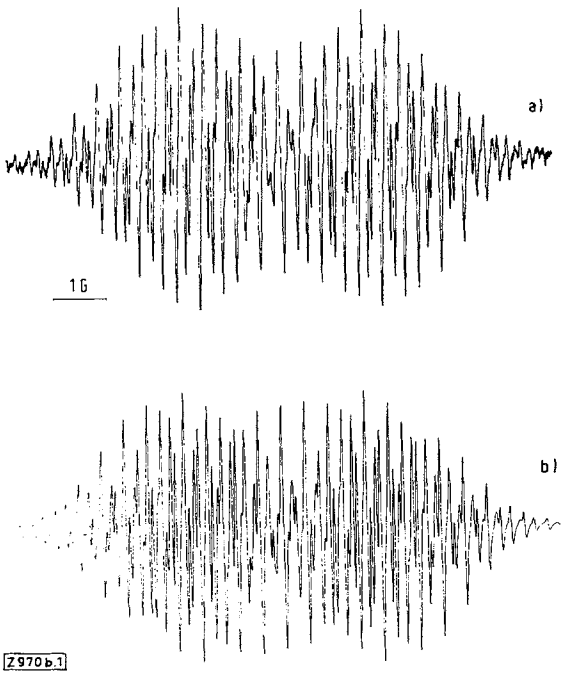


Fig. 1. a) ESR spectrum of the 1,1-di-*tert*-butyl-2-methylallyl radical *(1b)* in benzene at 25 °C; b) computer simulation with the coupling constants given in the text, line width 0.04 G.

stants due to spin polarization are therefore expected to be of the order of 0.0 G for H_a and H_b. The considerably larger experimental values of 0.96 and 3.40 G must consequently arise from another mechanism, as underlined in particular by the exceptionally large ratio of 3.5 for the coupling constants of two protons attached to the same π center C^3. Coupling constant ratios of about 1 are usually found for such protons (allyl radical: 14.8/13.9[10]; radical anion of butadiene: 7.6/7.6[11]).

Interpretation of the exceptionally large coupling constant of 3.40 G requires an experimentally unequivocal assignment to H_a or H_b, which is currently in progress. Since the geometry of the C^3—H_b σ bond relative to the p orbital of the unpaired electron, which is important for π-σ interactions, is almost identical with that of the C—H_{ortho} σ bonds of the benzyl radical that is twisted through 90°[9], the contribution from π-σ delocalization should be of comparable size for H_b and H_{ortho}. As a^H_{ortho} is 0.91 or 0.82 G[9], we assign $a^H = 0.96$ G to H_b. The exceptionally large coupling constant $a^H = 3.40$ G can then be readily explained in terms of homohyperconjugation in twisted π radicals[2]. This interpretation is supported by quantum mechanical approximation calculations for the conformations A and B of the *n*-propyl radical comparable with *(1)* which yield values of 1.0[5], 2.0[6], or 0.2 G[7] for H_b, and 3.0[5], 3.24[6], or 4.37 G[7] for H_a.

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[1] Homohyperconjugation in Twisted π Radicals, Part 2. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie, as well as by Deutsche Shell AG and Chemische Werke Hüls.—Part 1: [2].

[2] *A. Berndt*, Tetrahedron Lett. *1969*, 5251.

[3] *G. A. Russell, G. W. Holland*, and *K. Y. Chang*, J. Amer. Chem. Soc. *89*, 6629 (1967); *G. A. Russell* in *E. T. Kaiser* and *L. Kevan:* Radical Ions. Wiley-Interscience, New York 1968, pp. 138—147.

[4] *H. Lemaire, A. Rassat*, and *P. Rey*, Chem. Phys. Lett. *2*, 573 (1968).

[5] *G. R. Underwood* and *R. S. Givens*, J. Amer. Chem. Soc. *90*, 3713 (1968).

[6] *G. R. Underwood, V. L. Vogel*, and *J. Iorio*, Mol. Phys. *25*, 1093 (1973).

[7] *Y. Ellinger, A. Rassat, R. Subra*, and *G. Berthier*, J. Amer. Chem. Soc. *95*, 2373 (1973).

[8] The production of *(1b)* corresponds to the formation of the 1,1-di-*tert*-butylbenzyl radical [9].

[9] *K. Schreiner* and *A. Berndt*, Angew. Chem. *86*, 131 (1974); Angew. Chem. internat. Edit. *13*, 144 (1974).

[10] *R. W. Fessenden* and *R. H. Schuler*, J. Chem. Phys. *39*, 2147 (1963).

[11] *D. H. Levy* and *R. J. Myers*, J. Chem. Phys. *41*, 1062 (1964); *44*, 4177 (1966).

Bis(*N*,*N'*-methylsilanetriyl)tris(sulfur Diimide)—A Bicyclic Derivative of S_4N_4[**]

By *Herbert W. Roesky* and *Hartmut Wiezer*[*]

The sulfur atoms of tetrasulfur tetranitride can be replaced in part by metal atoms[1]. We now report the synthesis of a new cage compound in which two Si atoms are linked *via* three SN_2 bridges.

Reaction of methyltrichlorosilane with *N*,*N'*-bis(trimethylstannyl)sulfur diimide[2] *(1)* yields an ether-soluble yellow crystalline compound *(2)*,

$$\underset{(1)}{2CH_3SiCl_3 + 3(CH_3)_3Sn{-}NSN{-}Sn(CH_3)_3} \rightarrow \underset{(2)}{CH_3Si(NSN)_3SiCH_3} + 6(CH_3)_3SnCl$$

whose composition is established by elemental analysis and above all by its mass spectrum[3]. The molecular ion M^+ at *m/e* 266 has a relative intensity of 100%; the following fragments are also observed: 251 M−CH_3 (63%), 223 M−CH_3Si (5%), 220 M−NS (5%), 206 M−N_2S (5%), 192 M−N_3S (76%), 191 $CH_3Si_2N_4S_2$ (20%), 177 $CH_3Si_2N_3S_2$ (2%), 164 $(CH_3)_2SiN_3S_2$ (32%), 160 $(CH_3)_2Si_2N_3S$ (42%), 149 $CH_3SiN_3S_2$ (42%), 146 $(CH_3)_2Si_2N_2S$ (30%), 145 $CH_3Si_2N_3S$ (9%), 118 $(CH_3)_2SiN_2S$ (20%), 105? (12%), 103 CH_3SiN_2S (11%), 102 SiN_3S (18%), 101? (20%), 85 CH_3SiN_3 (41%), 74 SiNS (22%), 70 SiN_3 (60%), 58 $(CH_3)_2Si$ (20%), 46 NS (34%), 43 CH_3Si (40%).

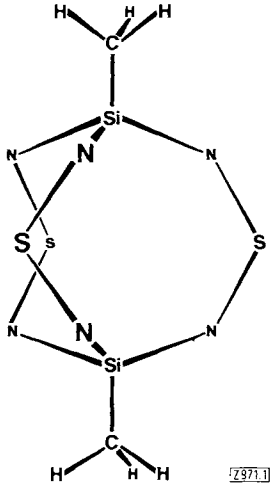


Fig. 1. Proposed structure of bis(*N*,*N'*-methylsilanetriyl)tris(sulfur diimide) *(2)*.

Compound *(2)* can be sublimed (sublimation temp. 65 °C/0.1 torr) and melts at 95—96 °C. The ^{1}H-NMR spectrum contains just one signal at δ = −0.50 ppm (TMS as external standard).

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The IR spectrum exhibits few bands and is suggestive of a symmetrical molecule [tentative assignment: ν_{as}CH 2980 w, ν_sCH 2930 w, δCH 1400 w, ν_{as}NS 1312 vs, ν_sNS 1190 vs cm^{-1}; the absorptions at 1270 m, 812 s, and 780 s cm^{-1} are not open to unequivocal interpretation].

To summarize our findings we suggest a structure having C_{3h} symmetry for compound *(2)* (Fig. 1). Models show the sulfur atoms of the eight-membered ring to have *exo-* and *endo* orientations and thus to be at a maximum distance from each other. Hence strain-free bonding is possible.

Experimental:

A solution of CH_3SiCl_3 (2.98 g, 2 mmol) in ether (50 ml) is added dropwise to a stirred solution of *(1)* (11.61 g, 3 mmol) in ether (250 ml). After refluxing for 3 h the solvent and $(CH_3)_3SnCl$ are removed under vacuum and the residue is sublimed. Yield of *(2)*: 1.1 g (44%) of yellow transparent leaflets.

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[1] *O. J. Scherer* and *R. Wies*, Angew. Chem. *83*, 882 (1971); Angew. Chem. internat. Edit. *10*, 812 (1971); *H. W. Roesky* and *H. Wiezer*, Chem. Ztg. Chem. App., in press.

[2] *H. W. Roesky* and *H. Wiezer*, Angew. Chem. *85*, 722 (1973); Angew. Chem. internat. Edit. *12*, 674 (1973).

[3] We are grateful to Dr. *D. Böhler*, Göttingen, for recording the spectrum.

Triphenylcyclotriphosphane as a New Ligand in Transition Metal Complexes[**]

By *Marianne Baudler* and *Manfred Bock*[*]

Following the synthesis of triphenylcyclotriphosphane *(1)*[1], the first established[2] derivative of P_3H_3[3], we have now succeeded in incorporating this neutral[4] three-membered phosphorus ring as a ligand into transition metal complexes.

(η-Triphenylcyclotriphosphane)tetracarbonyliron(0) *(2)* and -tricarbonylnickel(0) *(3)* are formed on reaction of *(1)* with tetracarbonylirontetrahydrofuran *(4)*[5] and tetracarbonylnickel *(5)*, respectively.

$$(C_6H_5P)_3 + [M(CO)_{n-1}L] \xrightarrow{-L} [M(C_6H_5P)_3(CO)_{n-1}]$$
(1)

(4), M = Fe, L = THF *(2)*, M = Fe, $n = 5$
(5), M = Ni, L = CO *(3)*, M = Ni, $n = 4$

The golden red monomeric complex *(2)* is readily soluble in carbon disulfide, tetrahydrofuran, and benzene. On heating, carbon monoxide is liberated above 60 °C before melting occurs (≈110 °C). Even after a few days at −20 °C transition can already be observed to products of higher relative molecular mass and lower solubility.

Owing to its instability, especially in dilute solution at reduced pressure and towards $Ni(CO)_4$, the lemon yellow complex *(3)* cannot be obtained absolutely pure. It decomposes at room temperature with grey coloration within a few hours; even more rapid conversion with brown and black coloration is promoted by dissolution or warming, CO being liberated above 60 °C.

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The ^{31}P-NMR spectra of *(2)* and *(3)* provide unequivocal information about the symmetry and bonding of the three-membered ring phosphorus ligand. They each display a sharp singlet at δ = +4.8 and +15.8 ppm, respectively (benzene, 25 °C, 85% H_3PO_4 ext.)[6] not subject to splitting or broadening at low temperature (tetrahydrofuran, −70 °C). The complexes are thus diamagnetic and the three phosphorus atoms equivalent. *(1)* must therefore be bonded through the plane of the P_3 ring as a trihapto ligand[7] and act as donor for an electron pair. The upfield shift of the ^{31}P-NMR signal of *(2)* and *(3)* compared to that of pure *(1)* (δ = +3.4 ppm[1]) reveals that complex formation is associated with a weak additional shielding of the phosphorus, which should be interpretable in terms of the acceptor properties of this ligand leading to delocalization of electrons of the transition metal[8].

A qualitative explanation of the bonding in *(2)* and *(3)* invokes 1) overlapping of a free metal orbital of suitable symmetry with the doubly occupied lowest energy P_3 ring molecular orbital (C_{3v} symmetry), formed by combination of three P atomic orbitals, which is preferentially localized above the plane of the ring, and 2) back-donation from an occupied metal orbital to the corresponding antibonding unoccupied P_3 ring molecular orbital. The extent to which d hybrid components play a role in the P AOs and thus in the P_3 ring MOs requires further study.

The intact cyclic structure of the phosphane ligand is confirmed by the IR spectra of *(2)* and *(3)*; their shape in the ring vibration region 540—390 cm^{-1} is characteristic for that found for *(1)*. For *(2)* the νCO vibration range contains four well-separated bands of almost equal intensity (2043, 2012, 1975, 1940 cm^{-1}) which, assuming a trigonal-bipyramidal structure, indicate the three-membered ring ligand to have an equatorial position (C_{2v} symmetry). Two intense CO bands (2070, 1999 cm^{-1}) appear for *(3)* (C_{3v} symmetry), which essentially agree with those of the monophosphane complex $[Ni(CO)_3P(C_6H_5)_3]$[9].

Owing to the poor thermal stability of the new complexes, neither the molecular ion nor fragments formed by successive removal of CO are observed in the mass spectrum; with *(2)* the only ion of significant intensity at higher mass numbers is $(C_6H_5P)_3^+$.

(η-Triphenylcyclotriphosphane)tetracarbonyliron(0) (2)

Compound *(1)* (2.0 g, 6.17 mmol) in THF (50 ml) is refluxed with a fivefold stoichiometric amount of *(4)* [from $Fe(CO)_5$ (6.05 g, 30.88 mmol)] in THF (150 ml) with stirring for 12 h (color change from violet-red to red-brown). After concentration to 50 ml, the same amount of a freshly prepared solution of *(4)* in THF is added and the mixture heated for a further 12 h. The crude red product obtained on complete removal of the solvent in a vacuum is dissolved in benzene (50 ml) and chromatographed over silica gel (0.05—0.2 mm); an unknown brown substance (≈10%) which cannot be eluted with benzene appears as residue. Removal of the solvent from the eluate and drying in a high vacuum afford *(2)* as a foamy solid having a golden-red luster; yield 2.3 g (76%). M. W. 490 (osmometric in C_6H_6 (45 °C)).

(η-Triphenylcyclotriphosphane)tricarbonylnickel(0) (3)

Compound *(5)* (0.53 g, 3.10 mmol) is added from a one-way syringe to a suspension of *(1)* (1.0 g, 3.09 mmol) in *n*-pentane (10 ml) at room temperature. Liberation of CO ceases after about 1 h. In order to avoid conversion of *(1)* into pentaphenyl-cyclopentaphosphane, stirring is performed only towards the end of the reaction and for 0.5 h after completion of the reaction. After insoluble products (≈100 mg) have been

filtered off, and the solvent rapidly drawn off in a vacuum, there remains a bright lemon-yellow foamy solid whose ^{31}P-NMR spectrum and elemental analysis show it to consist of 90% of *(3)*; yield 1.3 g (90%). The decomposability in dilute solution rules out reproducible osmometric molecular-weight determinations; however, values obtained provide an indication of a monomeric structure for *(3)*.

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[1] *M. Baudler* and *M. Bock*, Z. Anorg. Allg. Chem. *395*, 37 (1973); *M. Baudler* and *P. K. Medda*, *ibid.*, in press.

[2] *A. H. Cowley*, *T. A. Furtsch*, and *D. S. Dierdorf*, Chem. Commun. *1970*, 523; *P. S. Elmes*, *M. E. Redwood*, and *B. O. West*, *ibid. 1970*, 1120.

[3] *M. Baudler*, *H. Staendeke*, *M. Borgardt*, and *H. Strabel*, Naturwissenschaften *52*, 345 (1965); *M. Baudler*, *H. Staendeke*, *M. Borgardt*, *H. Strabel*, and *J. Dobbers*, *ibid. 53*, 106 (1966); *M. Baudler*, *H. Staendeke*, and *M. Kemper*, Z. Anorg. Allg. Chem. *388*, 125 (1972).

[4] The compounds $K_2[M(CO)_{4-1}(PC_6H_5)_3]$. THF (M = Fe, Ni) having the anionic three-membered cyclic ligand $[(PC_6H_5)_3]^{2-}$, which are mentioned in ref. [8], prove to be complex mixtures containing not a single species with an intact P_3 ring skeleton (*M. Baudler* and *M. Bock*, Z. Naturforsch., in press.)

[5] *W. Strohmeier*, Angew. Chem. *76*, 873 (1964); Angew. Chem. internat. Edit. *3*, 730 (1964).

[6] The spectrum of *(3)* also contains some weak additional signals attributable to by-products; a detailed assignment will require further study.

[7] *F. A. Cotton*, J. Amer. Chem. Soc. *90*, 6230 (1968).

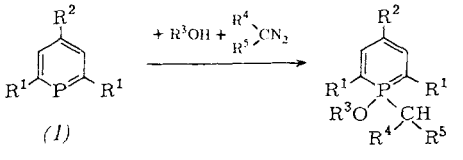
[8] Cf. the preferential formation of the cyclic dianion $[(C_6H_5P)_3]^{2-}$: *K. Issleib* and *E. Fluck*, Angew. Chem. *78*, 597 (1966); Angew. Chem. internat. Edit. *5*, 587 (1966).

[9] *L. S. Meriwether* and *M. L. Fiene*, J. Amer. Chem. Soc. *81*, 4200 (1959); *M. Bigorgne*, Bull. Soc. Chim. Fr. *1960*, 1985.

Reactions of λ^3-Phosphorins with Diazoalkanes in the Presence of Alcohols and Phenols

By *Peter Kieselack* and *Karl Dimroth*[*]

We report here on a new, versatile method for the synthesis of λ^5-phosphorins *(2)* having one C- *and* one-O-linked substituent on phosphorus in high yields from λ^3-phosphorins *(1)*[1].



(1) *(2)* (1)

The λ^5-phosphorins *(2)* are formed by reaction of *(1)* with diazoalkanes in the presence of alcohols or phenols. The reaction, which is initiated by a nucleophilic attack of the diazoalkane at the phosphorus atom, permits a wide range of possibilities as regards variation of the substituents on the phosphorin, on the hydroxy compound, and on the diazoalkane. Of particular interest is the reaction with diazoacetic ester, which leads to λ^5-phosphorins such as *(2k)* and *(2l)* having a reactive methylene group in the α-position to the phosphorus atom and thus opens up new synthetic possibilities. Equation (1) summarizes the course of the reaction.

Table 1 lists a few of the λ^5-phosphorins *(2)* that have been synthesized by this method.

4-Benzyl-1-methoxy-1-methyl-2,6-diphenyl-λ^5-phosphorin (2e)

An ethereal solution of diazomethane from nitrosomethylurea (300 mg, 3 mmol) is added with stirring at room temperature to a solution of 4-benzyl-2,6-diphenyl-λ^3-phosphorin (677 mg, 2 mmol) in benzene (25 ml) and methanol (10 ml). The reaction, which proceeds with strong evolution of nitrogen, is complete within a few minutes. Chromatography in benzene on silica gel and recrystallization from a little benzene/methanol affords 650 mg of *(2e)* [^{1}H-NMR (C_6D_6/TMS): δ = 1.6 (d, PCH_3), J_{P-H} = 14.5 Hz; 2.9 (d, $POCH_3$), J_{P-H} = 13.4 Hz; 3.75 (s, 2 benzyl-H); 6.9—7.6 (m, 17 aromatic H)].

Ethyl 1-(1-methoxy-2,4,6-triphenyl-λ^5-phosphorin)-acetate (2l)

A solution of 2,4,6-triphenyl-λ^3-phosphorin (1.3 g, 4 mmol) and ethyl diazoacetate (1 ml, *ca.* 10 mmol) in anhydrous benzene (50 ml) and absolute methanol (10 ml) is boiled under reflux. Further diazoester (4.5 ml) is added portionwise over a period of 30 h until λ^3-phosphorin can no longer be detected by thin-layer chromatography. Working up of the product as described above affords 1.4 g of *(2l)* [^{1}H-NMR (CCl_4/TMS): δ = 0.9 (t, $OCCH_3$), J_{H-H} = 7 Hz; 3.26 (d, PCH_2) J_{P-H} = 19 Hz; 3.35 (d, $POCH_3$), J_{P-H} = 14 Hz; 3.68 (q, OCH_2C), J_{H-H} = 7 Hz; 6.9—7.37 (m, 15 aromatic H); 7.63 (d, 3-H, 5-H), J_{P-H} = 31 Hz].

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[1] *K. Dimroth*, Fortschr. Chem. Forsch. *38*, 1 (1973).

Table 1. λ^5-Phosphorins *(2a)*—*(2l)*.

(2)	R^1	R^2	R^3	R^4	R^5	M.p. [°C]	Yield [%] [a]
a	C_6H_5	C_6H_5	CH_3	H	H	amorphous	81
b	C_6H_5	C_6H_5	$CH(CH_3)_2$	H	H	161—164	53
c	C_6H_5	C_6H_5	mesityl	H	H	104—106	77
d	C_6H_5	C_6H_5	CH_3	C_6H_5	C_6H_5	203—205	23
e	C_6H_5	CH_2—C_6H_5	CH_3	H	H	127—128	82
f	C_6H_5	CH_2—C_6H_5	C_2H_5	H	H	92—94	56
g	C_6H_5	CH_2—C_6H_5	$CH(CH_3)_2$	H	H	109—110	48
h	C_6H_5	CH_2—C_6H_5	*p*-cresyl	H	H	145—147	87
i	C_6H_5	CH_2—C_6H_5	C_6H_5	H	H	147—149	77
j	C_6H_5	CH_2—C_6H_5	CH_3	C_6H_5	C_6H_5	120—121	65
k	C_6H_5	CH_2—C_6H_5	CH_3	CO—OC_2H_5	H	103—105	71
l	C_6H_5	C_6H_5	CH_3	CO—OC_2H_5	H	147—150	78

[a] Referred to λ^3-phosphorin, not optimized, pure crystalline compound after chromatographic purification.

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Kinetic Investigation of Peptide Coupling[**]

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Very little has so far been published on the kinetics of individual peptide coupling reactions[1], though a knowledge of such is always essential in the optimization of peptide syntheses. To the best of our knowledge IR spectroscopy has not previously been used for such investigations. The principle can be illustrated with a few examples. In peptide syntheses with symmetric anhydrides[2] the anhydride band at 1810—1820 cm^{-1} becomes weaker, while an amide band appears between 1640 and 1700 cm^{-1}.

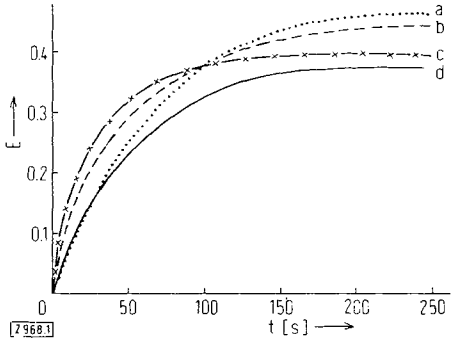


Fig. 1. Trace of coupling reactions by the "stop-flow" method in the region of the amide band (1635—1645 cm^{-1}). Total concentration of reagents: 10^{-2} mol/l in methylene chloride. PEG = polyethylene glycol. In brackets: relative reaction rate $v_{rel.}$. a) Dibutylamine + Boc-Pro-anhydride (1.00); b) H-Gly-OC_2H_5 + Ac_2O (1.64); c) H-Pro-PEG [4] + Ac_2O (2.57); d) Dibutylamine + Ac_2O (1.36). Equal volumes of the reaction solutions were fed together by means of a dual-piston pump into an an arrow-shaped mixing block and pumped through the flow cuvette (layer thickness 0.2 mm, NaCl).

Figures 1 and 2 show the kinetic course of a few coupling (*N*-acylation) reactions. The change in the amide and anhydride band, respectively, for each reaction is plotted against

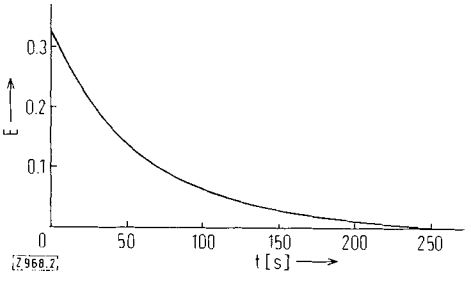


Fig. 2. Kinetic course of the coupling reaction H-Gly-Ala-Pro-PEG (10^{-2} mol/l) + Ac_2O (10^{-2} mol/l). Trace of the anhydride band at 1820 cm^{-1}. $v_{rel.}$ (referred to reaction a in Fig. 1) = 1.11.

time. As expected, both curves yield the same rate constants. For the determination of relative coupling rates $v_{rel.}$, measurements can be performed in a concentration range from 10^{-1} to 10^{-3} mol/l. For absolute rate constants a calibration curve must be recorded and the measurements carried out at higher dilution.

The change in the absorption bands can be measured directly in the reaction solution by a flow technique. This method is thus also suitable for monitoring heterogeneous reactions *e.g.* peptide syntheses on solid supports[3]. The simplicity of the procedure would suggest far reaching possibilities for the application of IR spectroscopy to kinetic investigations.

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[1] *J. J. Maher, M. E. Furey*, and *L. J. Greenberg*, Tetrahedron Lett. *1971*, 27; *R. H. Andreatta* and *H. Rink*, Helv. Chim. Acta 56, 1205 (1973); *E. Bayer, M. Mutter, R. Uhmann, J. Polster* and *H. Mauser*, J. Amer. Chem. Soc., in press.

[2] *H. Schüssler* and *H. Zahn*, Chem. Ber. 95, 1076 (1962); *H. Hagenmaier* and *H. Frank*, Hoppe-Seylers Z. Physiol. Chem. *353*, 1973 (1972).

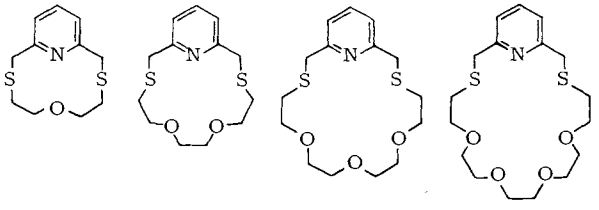
[3] *R. B. Merrifield*, Advan. Enzymol. *32*, 221 (1969).

[4] *M. Mutter, H. Hagenmaier*, and *E. Bayer*, Angew. Chem. *83*, 883 (1971); Angew. Chem. internat. Edit. *10*, 811 (1971); *M. Mutter* and *E. Bayer*, Nature *237*, 512 (1972); Angew. Chem. *86*, 101 (1974); Angew. Chem. internat. Edit. *13*, 88 (1974).

Novel Ligand Systems for Complexing Alkali Metal Ions[**]

By *Fritz Vögtle* and *Edwin Weber*[*]

Two fundamental types of neutral ligand systems for the specific complexing of alkali metal and alkaline earth metal salts have been described in the last few years: crown ethers[1, 2] and cryptating agents[3, 2]. In the continuation of our studies on medio- and macrocyclic polyethers[4] we have discovered a series of novel ligand systems *(1)*—*(4)*, which specifically complex alkali metal ions. The new ligand systems are readily accessible under dilution-principle conditions without use of the "template effect"[2].



(1) *(2)* *(3)* *(4)*

While *sodium* permanganate is instantaneously solubilized by *(2)* (m.p. 90—91 °C; δ = 3.96) and *(3)* (m.p. 58—59 °C; δ = 3.87)[5, 6], remarkably, $KMnO_4$ remains completely undissolved. In contrast to *(2)*, *(3)* also renders $NaMnO_4$ soluble in benzene. Lithium, rubidium, cesium, ammonium, and silver salts are not solubilized by *(2)* and *(3)* in organic solvents.

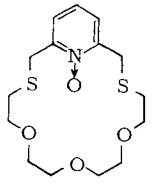
Addition of sodium iodide to solutions of *(3)* in $CDCl_3$ leads to a down-field shift of the characteristic α-CH_2 singlet by about 0.15 ppm; an intense band appears at 1640 cm^{-1} in the IR spectrum, and in the UV region a new band is observed at 243 nm, apart from the ligand absorption at λ = 273 nm.

In view of the observed Na^+-specificity of compounds *(2)* and *(3)* it is interesting to note the structural characteristics that deviate from those of the usual crown ethers and cryptate ligands; a) the *meta*-bridged aromatic ring, b) the sp^2 nitrogen as potential donor atom, and c) the heteroatom *beta* to the aromatic ring. Highly informative is a comparison of the 18-membered cycles *(3)*, *(5)* (colorless viscous oil, δ = 4.25) and *(6)* (colorless viscous oil; δ = 4.01) with [18]crown-6, dibenzo[18]crown-6, and dicyclohexyl[18]crown-6[1, 2], which

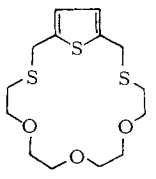
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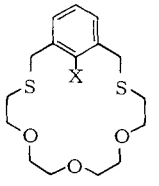
have the same number of ring members and which, in addition to complexing sodium, rubidium, and cesium, also complex potassium. *(5)* solubilizes $NaMnO_4$ in chloroform and benzene even more readily than *(3)*. Remarkably, *(5)* is the only 18-membered ring compound described here which also solubilizes *potassium* permanganate, albeit not to the same extent as $NaMnO_4$. The thiophenophane *(6)*, on the other hand, shows a much lesser tendency to complex sodium ions; even trace amounts of $KMnO_4$ are not solubilized in chloroform.



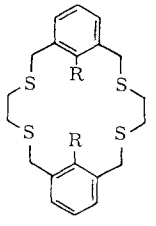
(5)



(6)

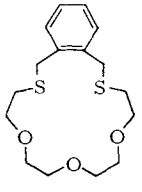


(7a), X = H
(7b), X = OCH_3

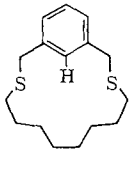


(8), R = OCH_3

In the transition from *(3)* to cyclophane *(7a)* (m.p. 56—57 °C; $\delta = 3.88$) the ability to solubilize $NaMnO_4$ in benzene—but not in chloroform—is lost. Interestingly, we have now found that the ability to solubilize $NaMnO_4$ in benzene reappears in the presence of a cyclophane such as *(7b)* (colorless viscous oil; $\delta = 3.87$) containing an intraannular methoxy group. It can thus be concluded that the pyridine nitrogen in *(3)*, the OCH_3 group in *(7b)*, and the pyridine *N*-oxide oxygen in *(5)* participate in the specific complexation of sodium ions; potassium ions (*e.g.* in $KMnO_4$) are complexed neither by *(6)* nor by *(7a)* and *(7b)*. In this connection, it is also interesting to note that the two OCH_3 groups in *(8)*[7], in association with the four sulfur atoms of the 18-membered ring, do not effect solubilization of $NaMnO_4$ and $KMnO_4$ in chloroform or benzene.



(9)



(10)

While the 17-membered orthocyclophane *(9)* (m.p. 47—49 °C; $\delta = 4.03$) also promotes solubilization of $NaMnO_4$—but not $KMnO_4$—in organic solvents (chloroform, less so in benzene), absence of the pyridine nitrogen and bridgeoxygen atoms as in *(10)* (m.p. 76—79 °C; $\delta = 3.87$) results, as expected, in a complete loss of complexing abilities[8].

Received: November 23, 1973 [Z 963 IE]
German version: Angew. Chem. *86*, 126 (1974)

[1] Review: *C. J. Pedersen* and *H. K. Frensdorff*, Angew. Chem. *84*, 16 (1972); Angew. Chem. internat. Edit. *11*, 16 (1972).

[2] Review: *F. Vögtle* and *P. Neumann*, Chem.-Ztg. *97*, 600 (1973).

[3] Reviews: *B. Dietrich, J. M. Lehn*, and *J. P. Sauvage*, Chem. Unserer Zeit 7, 120 (1973); *J. M. Lehn*, Struct. Bonding *16*, 1 (1973).

[4] *F. Vögtle* and *M. Zuber*, Tetrahedron Lett. *1972*, 561.

[5] Elemental analyses, mass spectra, proton resonances of the new cyclic species described here are in accord with the given structures. In each case the NMR signal of the α-CH_2 proton is quoted.

[6] IUPAC nomenclature for *(2)*: 6,9-dioxa-3,12-dithia-18-azabicyclo[12.3.1]octadeca-1(17),14(18),15-triene; for *(3)*: 6,9,12-trioxa-3,15-dithia-21-azabicyclo[15.3.1]heneicosa-1(20),17(21),18-triene. Phane nomenclature for *(2)*: 5,8-dioxa-2,11-dithia[12](2,6)pyridinophane; for *(3)*: 5,8,11-trioxa-2,14-dithia[15](2,6)pyridinophane.

[7] *F. Vögtle* and *P. Neumann*, Tetrahedron *26*, 5299 (1970).

[8] Note added in proof (January 14, 1974): Of the cycles *(1)* (m.p. 133—135 °C; $\delta = 3.97$) and *(4)* (colorless oil; $\delta = 3.93$) which have, in the meanwhile, been obtained in pure form, only *(4)* solubilizes $NaMnO_4$ in chloroform; $KMnO_4$ and $BaMnO_4$ are not solubilized. *(7c)*, X = —C≡N (m.p. 72—74 °C; $\delta = 4.17$) behaves similarly to *(7a)*. The complexing properties of the disulfone (m.p. 251—253 °C; $\delta = 4.48$) obtainable from *(7a)* resemble those of the sulfide.

Oxidative Decarbonylation of Octaethyl-α-hydroxyporphinatozinc(II)[**]

By *Siegmund Besecke* and *Jürgen-Hinrich Fuhrhop*[*]

Metalloporphyrins are oxidized *in vitro* by hydrogen peroxide[1] or molecular oxygen[2] to hydroxy compounds [*e.g. (1b)*], which have also been detected as primary products in the biological degradation of heme to biliverdin[3]. All that is known about the subsequent reaction of α-hydroxyheme with molecular oxygen to give biliverdin is that, in biological systems[4], the α-methine carbon atom of the porphyrin undergoes oxidation and cleavage as carbon monoxide. We report here on a novel photoreaction in which octaethyl-α-hydroxyporphinatozinc(II) *(1b)* is transformed, with loss of one molecule of carbon monoxide, into a compound containing a biliverdin residue.

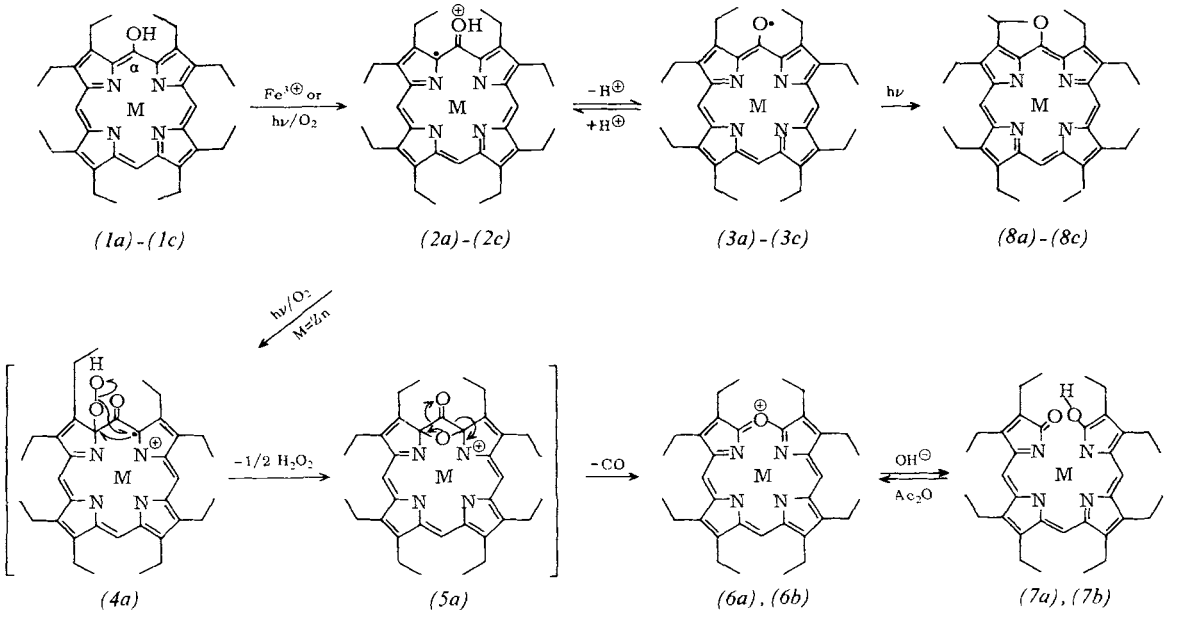
Irradiation of *(1b)* in benzene/methylene chloride in presence of air with visible light leads to formation of a π-radical *(2b)*, *(3b)*[5], which converts into a species lacking an intense Soret band [electron spectrum: 662 nm (32000), 394 (27000)] and exhibiting a pronounced diamagnetic ring current [NMR: methine H: $\delta = 9.18$ (2H), 9.27 (1H)]. These findings, the molecular ion peak at $m/e = 600$, and the absence of a carbonyl absorption in the IR spectrum, point to a porphyrin *(6b)* in which a methine group has been replaced by an oxygen atom whose unpaired electrons participate in the conjugative system of the macrocycle. Hence the structure of the octaethyl-α-hydroxyporphinatozinc(II) ion *(6b)* (iron analog, see [1, 6]).

Treatment of a methanolic solution of *(6b)* with a slight excess of potassium hydroxide leads, within a few minutes, to quantitative yields of the compound *(7b)* with biliverdin skeletal structure. With acetic anhydride this reaction was reversible. On passage of nitrogen through the solution in which the reaction *(2b)* → *(6b)* had been carried out, an amount of CO (80—90%) approximately equivalent to the amount of porphyrin could be detected in the escaping gas stream, whereas the test for CO_2 was negative *(Dräger tubes)*.

Irradiation of the nickel compound *(1c)* in the presence of oxygen under analogous conditions also led to initial forma-

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[**] This work was supported by the Deutsche Forschungsgemeinschaft.



(a), M = 2 H; (b), M = Zn; (c), M = Ni

tion of a π-radical (2c), (3c); however, in this case no subsequent addition of oxygen took place but rather conversion into the cyclic ether (8c) in high yield. The same cyclization reaction takes place with the zinc complex radical (2b) if irradiation is carried out in the absence of oxygen.

Metalloporphyrin compounds without substituents on the methine bridges react with oxygen and light to give formylbiliverdins, *i.e.* the methine carbon atom remains as component of a formyl group during cleavage of the macrocycle[7]. We ascribe this diverse behavior to the fact that the initial hydroperoxide of type (4), presumably formed in both cases, cannot form a dioxetane ring with the methine carbon atom in the case of the hydroxyporphyrins, and a hydroxyl radical is cleaved off instead.

We believe that the sequence (2b)→(6)→(7b) reproduces the essential degradation reactions of natural hydroxyheme and, because of the easily monitorable reaction conditions, uniform reaction course, and use of molecular oxygen as oxidizing agent, that it is a far more suitable model system than the previously used Warburg system[1, 6], which probably contains hydrogen peroxide.

Received: November 28, 1973 [Z 962 IE]
German version: Angew. Chem. 86, 125 (1974)

[1] *R. Bonnett* and *M. J. Dimsdale*, J. C. S. Perkin I *1972*, 2540.

[2] *K. M. Smith*, *G. H. Barnett*, *M. F. Hudson*, and *S. W. McCombie*, J. C. S. Perkin I *1973*, 691.

[3] *T. Kondo*, *D. C. Nicholson*, *A. H. Jackson*, and *G. W. Kenner*, Biochem. J. *121*, 601 (1971).

[4] *T. Sjostrand*, Scand. J. Clin. Lab. Invest. *1*, 201 (1949); *R. Troxler*, Biochemistry *11*, 4235 (1972).

[5] *J.-H. Fuhrhop*, *S. Besecke*, and *J. Subramanian*, J. C. S. Chem. Comm. *1973*, 1.

[6] *A. H. Jackson*, *G. W. Kenner*, and *K. M. Smith*, J. Chem. Soc. *C 1968*, 302; *O. Warburg* and *E. Negelein*, Ber. Deut. Chem. Ges. *63*, 1816 (1930).

[7] *J.-H. Fuhrhop* and *D. Mauzerall*, Photochem. Photobiol. *13*, 453 (1971); *P. K. W. Wasser* and *J.-H. Fuhrhop*, Ann. N. Y. Acad. Sci. *206*, 533 (1973).

ABSTRACTS

Reviews

Abstracts of selected progress reports and review articles

The metabolism of hormones, drugs, and other substances by the gut is discussed in a paper by *K. Hartiala*. These substances can be modified by non-synthetic reactions such as oxidation, reduction, and hydrolysis or by synthetic reactions for instance by conjugation with other residues, so as to fulfill special requirements in the body. Individual sections are devoted to the activity of intestinal microorganisms, to steroid metabolism, and to the adaptability of the gut. [Metabolism of Hormones, Drugs, and Other Substances by the Gut. Physiol. Rev. *53*, 496—534 (1973); 372 references]

[Rd 673 IE—R]

The metabolism and function of vitamin D is discussed in an article by *J. L. Omdahl* and *H. F. DeLuca*. The metabolism and function of vitamin D, whose vitamin nature arose as a result of civilization, are dynamically interrelated; this complex system plays the major role in controlling the concentration of calcium and phosphate in the body. [Regulation of Vitamin D Metabolism and Function. Physiol. Rev. *53*, 327—372 (1973); 231 references]

[Rd 672 IE—R]

The transformation of mammalian cells by two DNA tumor viruses is accompanied, as *R. O. Brady*, *P. H. Fishman*, and *P. T. Mora* have found, by a reduction in both the content of higher ganglioside homologs and the activity of the enzyme hematoside *N*-acetylgalactoseaminyl transferase. These changes are related reversibly with changes in growth properties. With both viruses the synthesis of the enzyme is possibly suppressed by a common repressor or impaired by the special

nature of the attachment of the virus to the cell genome. Similar changes in distribution and synthesis of gangliosides have been observed in the transformation by RNA viruses. [Membrane Components and Enzymes in Virally Transformed Cells. Fed. Proc. *32*, 102—108 (1973); 34 references]

[Rd 671 IE—R]

The effects of hormones on enzyme levels in the mammalian organism is discussed in an article by *H. C. Pitot* and *M. B. Yatvin*. In their function, the hormones can be compared with the inducers and repressors of microorganisms. Very little is known, however, about the mode of action of the hormones on the enzyme content of the cell. The authors deal, *inter alia*, with the influences of amine, steroid, and polypeptide hormones. [Interrelationships of Mammalian Hormones and Enzyme Levels *in Vivo*. Physiol. Rev. *53*, 228—325 (1973); 932 references]

[Rd 674 IE—R]

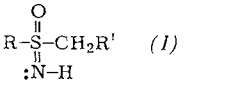
The cytological chemistry and physiology of blue-green algae are surveyed in a paper by *C. P. Wolk*. After reviewing the structure and chemical composition of cell walls and outer layers, membranes, and intracellular components, the author turns his attention to metabolism: photosynthesis, respiration, and metabolism of carbon, nitrogen, and sulfur. The final section is concerned, *inter alia*, with the genetics, motility, regulation and development phenomena, and the relationship of these microorganisms with other algae. [Physiology and Cytological Chemistry of Blue-Green Algae. Bacteriol. Rev. *37*, 32—101 (1973); 839 references]

[Rd 675 IE—R]

Chemical transmission in invertebrate central nervous systems has been studied by *H. M. Gerschenfeld*. Because of their size the neurons of many invertebrates offer experimental advantages over those of vertebrate animals; the investigated processes and compounds are, in principle, similar in vertebrate animals. Central nervous systems and neuromuscular junctions, their microanatomy, their physical properties, and the transmittive nature of a few compounds are discussed on the basis of well investigated taxa. [Chemical Transmission in Invertebrate Central Nervous Systems and Neuromuscular Junctions. Physiol. Rev. *53*, 1—119 (1973); 973 references]

[Rd 676 IE—R]

Sulfoximides and their derivatives as reagents for organic syntheses are considered by *C. R. Johnson*. Sulfoximides of type *(1)* are exceptionally versatile in their reactions and are potentially asymmetric. They are suitable for the synthesis of oxiranes, aziridines, cyclopropanes, alcohols, and alkenes. Apart from the alkenes, all these compounds can be obtained in optically active form from chiral sulfoximides. [The Utilization of Sulfoximines and Derivatives as Reagents for Organic Synthesis. Accounts Chem. Res. *6*, 341—347 (1973); 31 references]



(1)

[Rd 689 IE—L]

The surface of mammalian cells has been investigated by *M. M. Burger* with the aid of plant agglutinins (lectins). In transformed cells and tumor cells growth control is interrupted; at the same time these cells are agglutinated more strongly than the corresponding starting cells by several lectins. Protease-treated cells behave similarly. During protease treatment the intracellular level of cyclic AMP decreases transiently; however, this can be counteracted and growth control restored by addition of the nucleotide. A change in cell surface, which manifests itself in increased agglutinizibility, and a phase low in cyclic AMP content can also be observed during normal mitosis. A working hypothesis is discussed, according to which growth control runs its course *via* processes on the cell surface. [Surface Changes in Transformed Cells Detected by Lectins. Fed. Proc. *32*, 91—101 (1973); 69 references]

[Rd 685 IE—R]

The enzymic dehydrogenation of lactate and ethanol has been studied by *J. J. Holbrook* and *H. Gutfreund*. Chemical, spectrophotometric and fluorometric methods jointly provide information about enzymic intermediates and their reactions. Results of the analysis of equilibrium and kinetics of partial reactions, of the participation of protons, and of experiments on chemical modification can be combined in a reaction scheme taking into consideration all viewpoints. [Approaches to the Study of Enzyme Mechanisms. Lactate Dehydrogenase. FEBS Lett. *31*, 157—169 (1973); 76 references]

[Rd 679 IE—R]

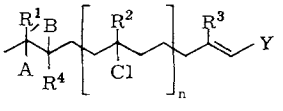
The nature of antigen receptors on the surfaces of lymphocytes is analyzed by *E. R. Unanue, H. D. Engers*, and *M. J. Karnovsky*. Most B cells (cells originating from bone marrow) carry on their surface on average 10^5 randomly distributed immunoglobulin molecules which are responsible for binding of the antigen. It is still unclear whether T cells (cells derived from the thymus) contain immunoglobulin molecules. They could not be detected in most of the T cells investigated. The thymus does contain a few cells with immunoglobulin on the surface; however, many of these do not react with antibodies against the alloantigen Θ. [Antigen Receptors on Lymphocytes. Fed. Proc. *32*, 44—47 (1973); 36 references]

[Rd 683 IE—R]

Patents

Abstracts of selected "Deutsche Offenlegungsschriften" (DOS), *i. e.* provisionally published specifications as filed with the German Patent Office

Unsaturated chlorine compounds *(1)* are suitable for the control of pests, particularly of invertebrates; they act by intervention in the hormone system of the animal organism. In insects, for example, the transformation to the imago, the laying of viable eggs, and the development of normal laid eggs are disturbed. They are practically non-toxic to vertebrates. The



(1)

compounds are readily broken down, and there is consequently no danger of cumulation. [DOS 2213177; F. Hoffmann-LaRoche & Co. AG, Basel]

[PR 140 IE—N]

Cobalt(II) complexes *(1)* or *(2)* are used as catalysts for aldol condensations. The complexes *(1)* ($n = 3$) can be prepared from cobalt(II) bipyridine complexes and hydrazines. Tris(hydrazinium chloride) complexes *(2)* are obtained from cobalt

$[Co(RNHNH_2)_n]X_2$ *(1)* $[Co(N_2H_4 \cdot HX)_3]X_2$ *(2)*

R = H, alkyl, aralkyl, aryl or haloaryl; X = halogen; $n = 2, 3$

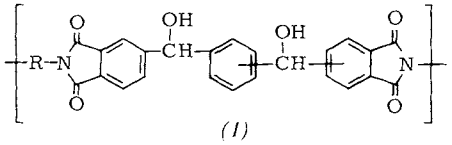
halide, hydroxylammonium halide, and a hydrazone. They are very readily soluble in water, and can be used as homogeneous catalysts in aqueous media. The complexes exhibit compound-specific properties. For example, cyclohexanone condenses quantitatively in the presence of $[Co(N_2H_4)_2]Br_2$ to form 2-(1-cyclohexenyl)cyclohexanone, whereas the polycondensation is promoted with the cobalt(II) chloride analog. [DOS 2166039; Cincinnati Milacron Chemicals, Reading (USA)]

[PR 127 IE—V]

As binders for the electric powder-spraying process, use is made of curable polymer powders of 1) 25—60 wt.% of styrene, α-methylstyrene, α-chlorostyrene, *p*-chlorostyrene, *p*-*tert*-butylstyrene, or mixtures of these; 2) 30—65 wt.% of acrylic esters with alcohol residues (C_{1-12}) or methacrylic esters with alcohol residues (C_{2-12}) or mixtures of these; 3) 0—25 wt.% of methyl methacrylate; 4) 4—20 wt.% of glycidyl (meth)acrylate; 5) 3—15 wt.% of (meth)acrylic, itaconic, maleic, or fumaric acid with an average molecular weight of 3000—20000. The polymer powder is still capable of running at a temperature of at least 50 °C, and has coalescence temperatures of 80 to 120 °C. This ensures smooth coalescence of the powder on the substrate to be coated. [DOS 2122313; Bayer AG, Leverkusen]

[PR 137 IE—Ö]

Heat-resistant polyimide or polyamide imide films are coated, in accordance with the invention, on at least one side with a thin adhesive layer of polyimides having the repeat grouping *(1)*. R is a bifunctional aliphatic, aromatic, carbocyclic or heterocyclic residue. The polyimide layer may contain a polar

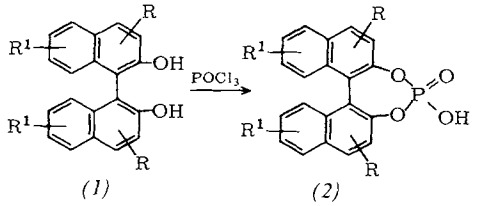


(1)

solvent. The adhesive films can be used for the bonding of printed circuits and for the sheathing of electric conductors, as well as for the production of composite materials. The bonding of the films to various supports can be carried out between 150 and 350 °C under a pressure of 0.01 to 1 kg/cm². [DOS 2221136, Rhône-Poulenc S. A., Paris]

[PR 144 IE—E]

Optical isomers of binaphthylylenephosphoric acids *(2)* and hydrogenated derivatives are suitable for the separation of



(1) *(2)*

R, R^1_4 = H, F, Cl, Br, alkyl (C_1—C_8), NO_2

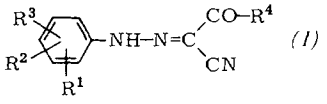
optically active organic bases into the optical antipodes and for the separation of *cis-trans* isomeric bases. They are prepared by reaction of binaphthyl-2,2'-diols *(1)* and phosphorus oxide chloride with subsequent resolution. [DOS 2212660; Richardson-Merrell, S.p.A., Naples]

[PR 157 IE—K]

For continuous perfluorination, perchlorinated compounds with trichloromethyl or pentachloroethyl groups and functional groups are allowed to react in the vapor phase with anhydrous hydrogen fluoride. Perchlorinated compounds containing further functional groups are compounds of this type that contain at least one ether, aldehyde, ketone, acyl chloride, or nitrile group, *etc.*, and that have no hydrogen that can be substituted by a chlorine atom. The reactants are led, under an absolute pressure of 1—4 bars, through a static catalyst bed consisting of three successive zones, in which the temperature increases by at least 10 °C between each pair of zones (first zone: 220—250 °C; second zone: 250—275 °C; third zone: 275—350 °C). All the chlorine atoms have been replaced by fluorine atoms *e.g.* in hexachloroacetone, trichloroacetyl chloride, octachlorobutanone, and trichloroacetaldehyde. [DOS 2221844; Rhône-Progil, Paris]

[PR 152 IE—J]

Hydrazones *(1)* are valuable insecticides, which are suitable *e.g.* for the control of species of Lepidoptera and mosquitoes, particularly in the larval form. They can be prepared by



(1)

R^1 = halogen, alkyl (C_1—C_4), alkoxy (C_1—C_4), CN, NO_2, CF_3, phenylazo, *p*-chlorophenoxy

R^2 = H, halogen, CF_3, alkyl (C_1—C_4)

R^3 = H, halogen

R^4 = halogen, α-naphthyl, 2-furyl, 2-thienyl

diazotization of anilines and reaction of the resulting diazonium salt with an aroylacetonitrile. [DOS 2222147; American Cyanamid Co. Wayne, N. J.]

[PR 141 IE—N]

The vulcanization of synthetic rubbers with high-energy radiation has not in the past led to products comparable with sulfur-vulcanized rubbers, since it was necessary to use excessively high radiation doses, which lead to overcuring and to side reactions, and are also uneconomical. By choice of certain synthetic rubbers and adjustment of the vulcanization conditions, qualitatively satisfactory vulcanized products can now be obtained by irradiation with doses of 0.5 to 7 megarad. The rubbers chosen are diolefin polymers and copolymers with weight average molecular weights of 50000 to 900000 and a molecular weight distribution of 1.01 to 30. Instructions are given for the distribution of the monomer units as a function of their contribution to the crosslinking. [DOS 2226106; The Firestone Tire & Rubber Co., Akron]

[PR 124 IE—S]

Biodegradable emulsifiers for polychloroprene. Octyl sulfate salts *(1)*, preferably with linear octyl chains, can be used as biodegradable emulsifiers for polychloroprene. The aqueous emulsion of the monomer material is prepared in the usual manner. *(1)* may be added either alone or in combination with known emulsifiers during any stage of the polymerization. The only condition is that it must be present at least during the acidification of the latex before coagulation. Approximately 0.05 to 2.0 parts by weight of *(1)* per 100 parts by weight of polymerizable monomer are generally used. Comonomers may also be used in addition to chloroprene if the content of comonomer is not greater than 25 mole %. [DOS 2210957, Petro-Tex Chemical Corp., Houston]

[PR 145 IE—E]

The ammonoxidation of olefins, particularly isobutylene, to form β-olefinic nitriles (methacrylonitrile) is carried out in the presence of a catalyst whose active component consists of 1—15 wt.% of MoO_3, 25—50 wt.% of Fe_2O_3, and 45—70 wt.% of TeO_3, and which is applied to a support such as kaolin, alumina, kieselgur, or silica. The reaction is carried out at 300—600 °C (preferably at 350—500 °C) in the presence of a static-bed catalyst or in a fluidized bed. The contact time with the catalyst is 0.5—15 s; the yields are satisfactory. [DOS 2210395; Société Nationale des Petroles d'Aquitaine, Courbevoie]

[PR 146 IE—J]

The selective isomerization of long-chain 1-olefins *(1)* to 2-olefins is carried out by bringing the 1-olefin into contact with a calcium metal/aluminosilicate/molecular sieve catalyst coated with a monoatomic layer of sodium. The temperature should be between the freezing point of the 1-olefin and 150 °C. About 70% (or more) of the 1-olefins can be isomerized in 10—15 min *e.g.* at room temperature and at atmospheric pressure. Example: conversion of 1-hexadecene (25 °C, 10 min)

$$CH_2=CH-CHRR^1 \qquad (1)$$

R^1 = *n*-alkyl
R^2 = any substituent that does not react with Na
Total number of C atoms: 6—25

into 88% of 2-hexadecene and 8% of 3-hexadecene; 4% of the starting material did not react. [DOS 2209379; Akzona Inc., Asheville]

[PR 147 IE—J]

BOOK REVIEWS

Electrochemistry. Vol. 2. Specialist Periodical Reports. By *G. J. Hills.* The Chemical Society, London 1972. 1st ed., viii, 299 pp., numerous formulae, bound £ 7

This second volume of the series presents a survey of the publications that appeared in 1970 in important areas of electrochemistry. The remarkable intensity of electrochemical reseach can be seen from the size of the book (despite a concise treatment of the individual facts) and from the 700 literature references from 1970 alone. Competent commentators deal with the synthetic aspects of organic electrochemistry (focal points: nucleophilic substitutions on aromatic compounds and olefins, reductive coupling and bond fissure, stereospecific electrode reactions), investigations on salt melts, and reactions at solid metal electrodes, as well as with the further investigation of the double layers at the phase boundaries between electrode and electrolyte. Recent developments in ion-specific membranes are presented in another chapter.

The presentation of the book and the printing, which is surprisingly careful in view of the quick publication are excellent. If the tempo and the quality can be maintained, the later volumes will be welcomed by grateful readers who wish to keep abreast of the general situation in electrochemistry.

Herbert Lehmkuhl [NB 167 IE]

Analytical Chemistry of Phosphorus Compounds. Edited by *M. Halmann.* John Wiley & Sons, Inc., New York—London 1972. 1st ed., x, 850 pp., numerous figures and tables, bound £ 16.80.

Phosphorus occupies a central position in both the animate and the inanimate worlds. The uses of phosphorus compounds in many areas of research and of life are correspondingly numerous. An essential condition for the development of phosphorus chemistry was the availability of efficient analytical methods.

Until now, the original publications and analytical findings have been scattered chaotically in the chemical literature. Workers in the phosphorus field will therefore welcome this compilation of the most important methods of separation, identification, and determination by a team of outstanding experts under the leadership of *M. Halmann.* Both the classical "wet methods" and the possibilities of modern spectroscopic techniques are discussed clearly and with reference to the literature. However, the specialist will be disappointed by the occasional repetitions and by the omission of practical hints and methods that have proved to be essential in the laboratory. It should be possible to eliminate these gaps in the second edition without upsetting the excellent arrangement of the book.

As an unselfish assistant to the advancing chemist, analysis has repeatedly paved the way for new knowledge. The publication of this monograph will therefore please workers in the phosphorus field.

Leopold Horner [NB 175 IE]

Ultracentrifugation of Macromolecules. By *J. W. Williams.* Academic Press, New York—London 1972. 1st ed., xvii, 118 pp., bound $ 9.50.

The present book has resulted from the copying of seminar lectures during the author's visiting professorship at the University of Uppsala.

It deals in great detail with the thermodynamics of ideal and non-ideal solutions and of chemical equilibrium under the influence of high gravitational accelerations. The various ways of taking the average of the molecular weights for polydisperse systems are also discussed. In the Appendix the reader finds an introduction to the theory of ultracentrifugation, and several solutions of the Lamm differential equation are discussed. The influence of polydispersity on the boundary layer in sedimentation velocity experiments is then dealt with.

The book contains evaluations and interpretations of experimental data on the molecular weights and sedimentation coefficients of synthetic macromolecules (polystyrene, dextran) and of natural macromolecules (β-lactoglobulin B, lysozyme, chromatrypsinogen A). The section on self-association in protein solutions can be strongly recommended.

There is unfortunately nothing in the book about the theory and possible applications of isopyknic ultracentrifugation as an equilibrium method, or about the band separation technique for sedimentation velocity experiments with the associated advantages (no Johnson-Ogston effect). Experimental details such as the various optical systems and the evaluation formulas are also omitted.

On the whole the book is of interest only to the analytical investigator, since there is no mention anywhere of modern techniques of preparative ultracentrifugation.

Paul Schmider [NB 177 IE]

Vibrational Spectroscopy of Solids. By *P. M. A. Sherwood.* Cambridge University Press, Cambridge 1972. 1st ed., xi, 254 pp., numerous figures, bound £ 5.90.

IR and Raman spectra of crystals reflect some of the properties of the structural elements, their interactions, as well as the whole lattice. In particular, the spectra recorded using single crystals with polarized radiation enable one to draw conclusions regarding the arrangement of the lattice units and their symmetry. Until now, the information necessary for the interpretation of these spectra has not been very widely known among chemists, and crystal spectra were often interpreted in the same way as the spectra of gases. Several authors have recently written accounts of this field for chemists. The author of the present work first points out the typical and possible differences in the spectra of molecules in the gas phase and in the solid state. He then discusses the dynamic properties of the crystal and their quantization, as well as the application of group theory. Chapters on the interaction of the radiation with the crystal and on second order effects then follow. Finally, the excitations that can be observed in addition to the vibrational transitions are discussed: excitons, magnons, and plasmons.

The author intentionally applies the theory only to very simple lattice units. Since difficulties arise in the application of the theory to more complicated molecules, it would have been useful to include spectra of this nature and to demonstrate their interpretation. A rather disturbing feature is the needless introduction of "Unit Cell Analysis" instead of "Factor Group Analysis". On the whole the text is very readable and comprehensible, and can be strongly recommended as an introduction.

Bernhard Schrader [NB 179 IE]

Quantenbiochemie für Chemiker und Biologen (Quantum Biochemistry for Chemists and Biologists). By *J. Ladik.* Ferdinand Enke Verlag, Stuttgart 1972. 1st ed., 252 pp., 111 figures and 11 tables, bound DM 19.80.

Quantum mechanics reduces not only the problems of chemistry (as stressed by *Dirac* in 1929) but also those of molecular biology to the solution of mathematical equations; the difference lies mainly in the complexity of biological systems. In this book, *Ladik* presents a survey of the biochemical problems that can be tackled with the aid of quantum-mechanical calculations and the nature of the results that can be obtained at the present time. After an introduction to the principles of quantum mechanics, without presupposing any existing knowledge of physics, chemistry, or biology, the author discusses in particular the relationships between the electronic structure and the biological properties of DNA; chapters on proteins, carcinogenic substances, and porphyrins then follow. A final look ahead outlines the possibilities of a molecular genetics and a molecular gerontology, as well as of the quantum-mechanical treatment of pharmaceutical problems.

The book seems excellently suited for arousing an interest in the connections between the current problems of molecular biology and the physical principles of quantum mechanics, and for providing a link between the languages of the biochemist and of the quantum chemist. In this light it does not seem an excessively serious fault that the selection of the literature is occasionally rather one-sided or that there are a few shortcomings in the German translation.

The book was not written for the specialist, but it can be recommended as readable and stimulating to all those who are interested in current questions of molecular biology outside their own field of work.

Martin Klessinger [NB 183 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal.

Ligandenfeldtheorie. By *P. Schuster.* Vol. 19 of the series "Chemische Taschenbücher". Edited by *W. Foerst* and *H. Grünewald.* Verlag Chemie, Weinheim 1973. ix, 192 pp., stitched DM 28.—.

Contents: Elektronenzustände; Elektronenwechselwirkung; Anwendung der Ligandenfeldtheorie auf Grundzustände von Komplexionen; Spin-Bahn-Kopplung; Spektren von Übergangsmetallkomplexionen im Rahmen der Ligandenfeldtheorie; Ligandenfeldtheorie im Rahmen anderer quantenchemischer Methoden.

Principles of Reaction Kinetics. By *P. G. Ashmore.* 2nd Edit., No. 9 of the series "Monographs for Teachers" The Chemical Society, London 1973. 78 pp., stitched 80 p.

Contents: Introductory Survey; Rates and Rate Laws for Elementary Reactions; Rate Laws for Some Complex Reactions; Chain Reactions; Résumé of Aims and Principles.

Chemical Instrumentation. A Systematic Approach to Instrumental Analysis. By *H. A. Strobel.* Addison-Wesley Publishing Company, Reading/USA 1973. 2nd Edit. xxii, 903 pp., bound $ 22.50.

Contents: Measurement and Instrumentation; Electronics; Optics; Spectrometric Methods; Electroanalytical Methods.

Progress in Bioorganic Chemistry, Vol. 2. Edited by *E. T. Kaiser* and *F. J. Kézdy.* John Wiley & Sons, New York—London 1973. xiii, 257 pp., bound £ 8.25

Contents: Reaction Kinetics in the Presence of Micelle-Forming Surfactants; The Apolar Bond; Mechanisms of Action of Folic Acid Cofactors; Catalytic Activity of Pepsin.

Eléments de Chimie Minérale. By *H. Wahl.* Masson et Cie., Editeurs, Paris 1973. xi, 174 pp., stitched 52 F

Contents: L'Air; L'Eau; Oxygène; Hydrogène Famille des Halogènes; Famille de l'Oxygène; Famille de l'Azote; Famille du Carbone; Famille du Bore.

Condensed Pyridazines Including Cinnolines and Phthalazines. Edited by *R. N. Castle.* Vol. 27 of the series "The Chemistry of Heterocyclic Compounds". Edited by *A. Weissberger* and *E. C. Taylor.* John Wiley & Sons, New York—London 1973. xii, 1124 pp., bound *ca.* £ 33.45.

Contents: Cinnolines; Phthalazines; Azolo- and Azinopyridazines; Oxa and Thia Analogs.

Electronen und Chemische Bindung. By *H. B. Gray.* de Gruyter Berlin—New York 1973. xi, 194 pp., stitched DM 24.—.

Contents: Elektronen in Atomen; Zweiatomige Moleküle; Lineare dreiatomige Moleküle; Trigonal-planare Moleküle; Tetraedrische Moleküle; Trigonal-pyramidale Moleküle; Gewinkelte dreiatomige Moleküle; Die Bindung in organischen Molekülen; Bindungen unter Beteiligung von d-Valenzorbitalen.

Gas and Liquid Chromatography Abstracts 1972. Edited by *C. E. H. Knapman* and *R. J. Maggs*. Applied Science Publishers Ltd. Barking, for the Institute of Petroleum, London 1973. xviii, 230, 21 pp., bound £ 8.00.

Physikalische Chemie. By *W. J. Moore*. de Gruyter, Berlin—New York 1973. Revised and expanded 4th Edith. xvi, 1134 pp., bound DM 78.—.

Selected Molecular Rearrangements. By *T. S. Stevens* and *W. E. Watts*. Van Nostrand Reinhold Company, London 1973. x, 212 pp., bound £ 5.50.

Contents: Nucleophilic Rearrangements; 1,2-Electrophilic Rearrangements; Alkali-Induced Rearrangements; Pericyclic Rearrangements; Aromatic Rearrangements.

Protein-Protein Interactions. Edited by *R. Jaenicke* and *E. Helmreich*. 23rd Colloquium of the Gesellschaft für Biologische Chemie, April 13—15, 1972 at Mosbach/Baden. Springer, Berlin—Heidelberg—New York 1972. viii, 646 pp., bound DM 78.—.

Contents: Quaternary Structure of Proteins; Approaches for Determining Protein Complexes; Heterologous Protein Interactions; Muscle; Multienzyme Complexes; Antigen-Antibody Interactions; Self-Assembly; Intercellular Interactions.

Progress in Surface and Membrane Science, Vol. 6. Edited by *J. F. Danielli, M. D. Rosenberg*, and *D. A. Cadenhead*. Academic Press, New York—London 1973. xiii, 280 pp., bound $ 22.50.

Contents: The Silver Halide Surface; The Mercury-Solution Interface; Contact-Angle Hysteresis; Ion Binding and Ion Transport; Cytomembranes; Interactions of Blood Proteins with Polymeric and Artificial Surfaces.

Fast Ion Transport in Solids. Solid State Batteries and Devices. Edited by *W. van Gool*. North-Hollans Publishing Company, Amsterdam 1973. xvi, 728 pp., bound Dfl. 100.00/$ 35.10.—Proceedings of the NATO Sponsored Advanced Study Institute on Fast Ion Transport in Solids, Solid State Batteries and Devices, Belgirate, Italy, September 5—15, 1972.

Hard and Soft Acids and Bases. Edited by *R. G. Pearson*. From the series "Benchmark Papers in Inorganic Chemistry". Edited by *H. H. Sisler*. Dowden, Hutchinson & Ross, Stroudsburg/USA 1973. xiii, 480 pp., bound $ 23.00.

Polymer Transition Temperature Data Sheets. Compiled by *W. A. Lee* and *R. A. Rutherford*. Rubber and Plastics Research Association of Great Britan, Shawbury Shrewsbury 1973. Loose-leaf book £ 10.00.

Addition and Elimination Reactions of Aliphatic Compounds. Vol. 9 of the series "Comprehensive Chemical Kinetics". Edited by *C. H. Bamford* and *C. F. H. Tipper*. Elsevier Amsterdam 1973. xiii, 515 pp., bound Dfl. 160.00/$ 56.10.

Contents: Electrophilic Additions to Unsaturated Systems; Addition of Unsaturated Compounds to Each Other; Elimination Reactions; Carbene and Carbenoid Formation and Reactions; Kinetics of Alkene Isomerizations.

Reviews in Macromolecular Chemistry, Vol. 9. Edited by *G. B. Butler, K. F. O'Driscoll*, and *M. Shen*. Marcel Dekker, New York 1973. v, 369 pp., bound $ 21.50.

Contents: Mathematical Modeling of Polymerization Reactions; Mechanical Properties of Polymers; Anionic Cyclopolymerization; Thermodynamics of Equilibrium Polymerization.

Applied Spectroscopy Reviews, Vol. 6. Edited by *E. G. Brame, Jr.*, Marcel Dekker, New York 1973. xiv, 375 pp., bound $ 21.50.

Contents: Spectra of Biopolymers; Infrared Fourier Transform Spectroscopy; Neutron Scattering and Vibrational Spectra of Molecular Crystals; Diagnostics of High-Temperature, High Density Plasma by Radiation Analysis; Spectroscopy of Liquid Crystals; Metals Analysis by Emission Spectroscopy.

Determination of Organic Structures by Physical Methods, Vol. 5. Edited by *F. C. Nachod* and *J. J. Zacherman*. Academic Press, New York—London 1973. xv, 367 pp., bound $ 26.00.

Contents: Electron Diffraction; Spin Saturation Labeling; Nuclear Polarization; Ion Cyclotron Resonance Spectroscopy; Nuclear Quadrupole Resonance; Mössbauer Spectra of Organometallics; Automated Chemical Structure Analysis Systems; NQR Applications in Organic and Metalloorganic Chemistry.

The Total Synthesis of Natural Products, Vol. 1. Edited by *J. A. Simon*. Wiley-Interscience, New York—London 1973. ix, 603 pp., bound £ 12.50.

Contents: Carbohydrates; Prostaglandins; Pyrrole Pigments; Nucleic Acids; Antibiotics; Oxygen Ring Compounds.

Advances in Organometallic Chemistry, Vol. 11. Edited by *F. G. A. Stone* and *R. West*. Academic Press New York—London 1973. xi, 510 pp., bound $ 27.00.

Contents: Boranes in Organic Chemistry; Transition Metal-Isocyanide Complexes; Carbon Monoxide Insertion Reactions; Organothallium Chemistry; Radiochemistry of Organometallic Compounds; Silicon-Transition Metal Complexes; Organocobalt(III).

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Results and Problems of *O*-Glycoside Synthesis

By Günter Wulff and Gerhard Röhle[*]

Considerable problems attend the synthesis of biologically important natural products whose carbohydrate components display a greater or lesser degree of complexity. The present progress report surveys recent developments in the formation of *O*-glycosidic bonds starting from 1-halo sugars and from sugar 1,2-orthoesters. Particular emphasis is placed on attempts to reach a better understanding of the steric course of glycosylation reactions on the basis of mechanistic considerations. Studies on the silver-salt dependence of the Koenigs-Knorr synthesis led to improvements in preparative applications and to new concepts concerning the reaction course. The introduction of sugar 1,2-orthoesters as glycosylation components has greatly enriched our preparative armoury for the synthesis of *trans* glycosides. Remarkable progress has also been made in the synthesis of *cis* glycosides, in part by exploiting novel neighboring group effects.

1. Introduction

In recent years a steadily increasing research effort has been centered on the production of glycosides, and particularly of oligo- and polysaccharides. Crucial impetus has come from the increasing interest shown by biochemists in these substances. The studies were directed above all to the glycoproteins, the immunoactive oligo- and polysaccharide moieties of bacterial cell walls and red blood cells, the glycolipids (*e.g.* cerebrosides and gangliosides), and antibiotics with carbohydrate constituents. Plant glycosides have also received due attention (*e.g.* cardiac glycosides, saponins, flavonoid glycosides). All these studies set a highly promising development in motion.

Whereas the methodological prerequisites are nowadays fulfilled for the synthesis of more complex compounds belonging to the class of oligo- and polypeptides, which were long at the forefront of scientific interest, many problems still await solution for the systematic construction of fairly long sugar sequences. In contrast to the peptides, not only can the sequence of the basic units vary but so can the site of linkage of two chain members and the configuration at the anomeric C atom. The diverse protecting groups required for such syntheses are already known in large numbers; however, the main obstacle lies in formation of the glycosidic linkage. The yields attained are usually rather modest, and steric control is difficult to achieve.

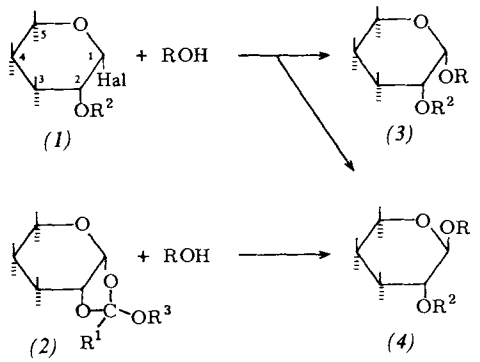
This report will therefore deal essentially with the problems of glycosidic bond formation *per se* from a methodological standpoint. We shall confine our attention exclusively to syntheses starting from 1-halo sugars (1-haloses) [*e.g. (1)*][***] and 1,2-orthoesters [*e.g. (2)*][***] which serve mainly for the preparation of *cis*- *(3)* and *trans* glycosides *(4)* of complex alcohols.

Methods for the preparation of glycosides of simple alcohols, *e.g.* alcoholysis of free sugars (Fischer synthesis)[1] and more specialized techniques starting from unsaturated sugars[1,2], 1-hydroxy sugars[3], 1-*O*-acyl sugars[1,4], sugar anhydrides[1,5], sugar dithioacetals[6,7], sugar thioglycosides[7a], and earlier studies will not be considered. Many of them are cited in the review literature[1,6–9]. Details of oligosaccharide[10–12]

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[***] In this and in a number of the following cases the formulas of the sugars are written generally, except for the substituent on C-2. They refer to pyranoid pentose or hexose derivatives whose other OH groups are not shown.



(1) (3) (2) (4)

and polysaccharide syntheses[5, 13] will be found in the pertinent references.

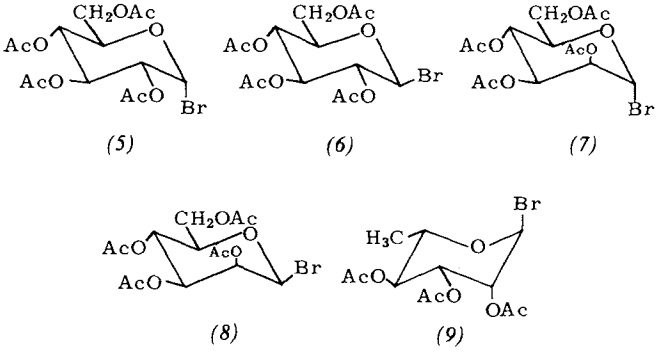
2. Possible Reaction Routes

2.1. General

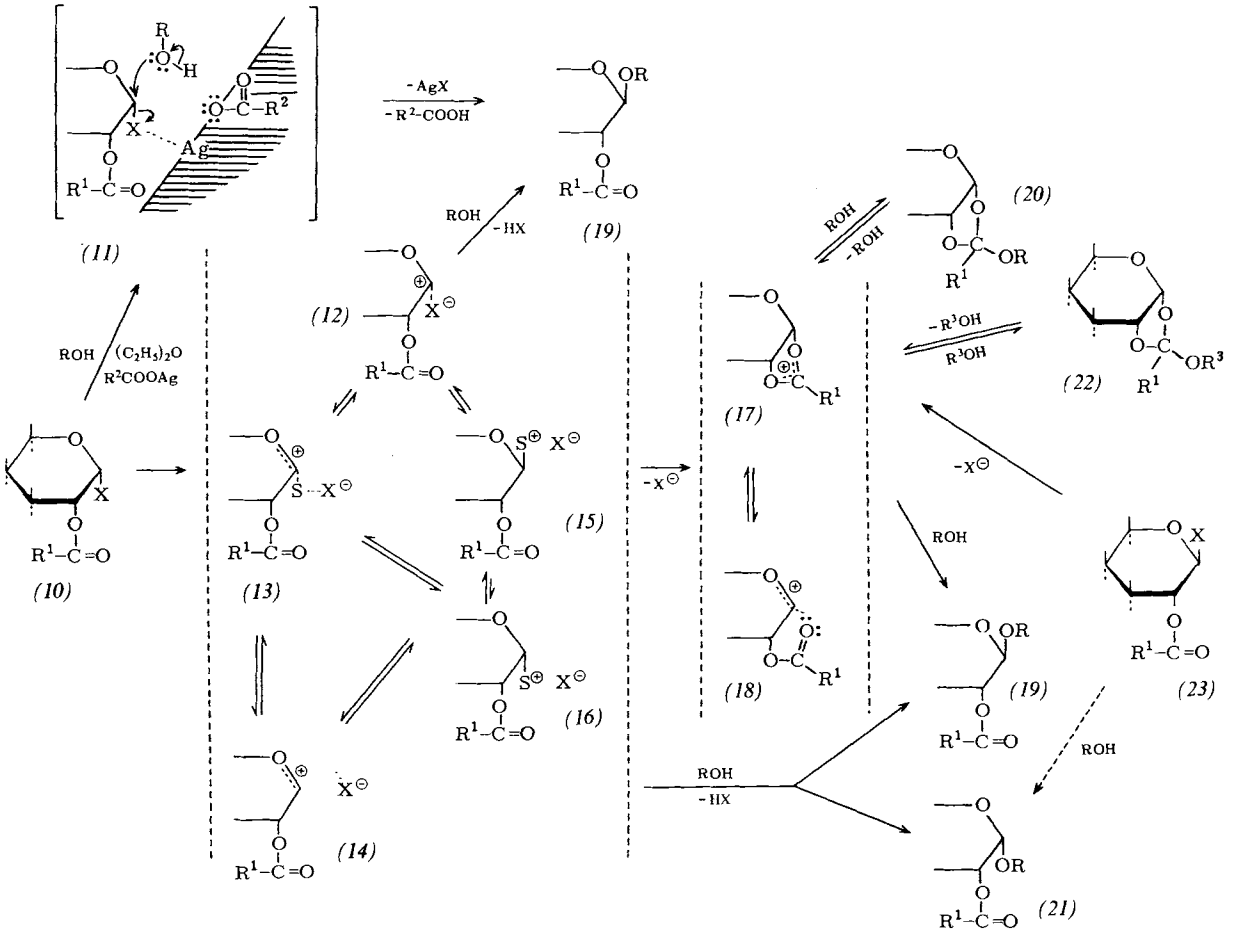
We shall begin with an attempt to classify the numerous glycosylation reactions starting from 1-haloses or orthoesters according to the probable mechanism. Only after having accrued this information can we explain the often surprising steric course of the reaction and the by-products formed, or recognize possibilities of increasing yields. The more preparative aspects will be considered in Sections 3, 4, 5, and 6.

Unfortunately only fragmentary data concerning the reaction mechanism of glycosylation reactions[14-16] have so far become available; only the solvolysis of 1-halo sugars has been studied in detail[16]. The schemes appearing in this report and the classification of reaction types are therefore based merely on a combination of literature data and our own results, and categorize some reactions preferentially according to their steric course. None of these mechanisms can be regarded as proved in a strict sense; the classification should consequently be viewed as a basis for discussion.

The acylated 1-halo sugars widely used in glycoside syntheses are usually obtained as the thermodynamically more stable form having an axial halogen on C-1. For the D-sugars existing mainly in the C-1 conformation [(5)—(8)] and the L-sugars occurring predominantly in the 1-C conformation [e.g. (9)], these will be the α-halides, e.g. 2,3,4,6-tetra-*O*-acetyl-α-D-glucosyl bromide (5) and -mannosyl bromide (7), as well as 2,3,4-tri-*O*-acetyl-α-L-rhamnosyl bromide (9)[17, 18].



(5) (6) (7) (8) (9)



Scheme 1. Reaction pathways of peracylated 1,2-*cis* (10) and 1,2-*trans* haloses (23) and 1,2-orthoesters (22) (S = solvent).

The corresponding β-halides having equatorial halogen [*e.g.* *(6)* and *(8)*] can only be prepared in kinetically controlled reactions; they are rather unstable and much more reactive than the α-halides. This is attributed to the anomeric effect, *i.e.* a destabilization arising from electrostatic interaction between the parallel p orbitals of oxygen and halogen[18,19]. Practically only chlorides and bromides are employed in glycoside syntheses.

The steric course of the glycosylation reaction of peracylated haloses is, however, determined not by the axial or equatorial orientation of the halogen but by its interaction with the neighboring substituent on C-2 of the halose. Glycosylation with the 1,2-*cis* haloses *(5)* and *(8)* generally proceeds with inversion at C-1 to give 1,2-*trans* glycosides of type *(4)*, whereas the 1,2-*trans* haloses *(6)*, *(7)*, and *(9)* afford 1,2-orthoesters under certain conditions but mainly 1,2-*trans* glycosides under others[15,20]. Hence 1,2-*cis* glycosides [type *(3)*] are relatively difficultly accessible from peracylated haloses. They generally have to be prepared by special techniques (see Sections 2.3 and 4).

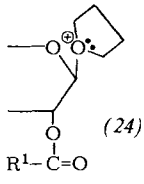
2.2. The Key Role of Acyloxonium Ions

The possible reaction pathways of peracylated 1,2-*cis* *(10)* and 1,2-*trans* haloses *(23)* and of 1,2-orthoesters *(22)* are depicted in Scheme 1[*].

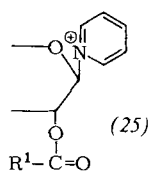
Preferential formation of *trans* glycosides *(19)* from *cis* haloses *(10)* with Walden inversion would be most readily explained by assuming an S_N2 mechanism[20]. However, available evidence indicates this mode to occur only rarely in glycosylation reactions. Our own studies show glycosylations in the presence of insoluble silver compounds (*e.g.* Ag_2CO_3, Ag_2O, silver 4-hydroxyvalerate) in certain solvents (particularly diethyl ether and probably also chloroform with iodine) at low temperatures to constitute a special case. Here the alcohol definitely participates in the rate-determining step of the reaction[21,22]. The halose adsorbed onto the silver compound undergoes a concerted reaction with the alcohol [cf. *(11)*]. This type of reaction requires solid silver compounds having a particular structure and solvents contributing to transition-state stabilization (see Section 3.1)[**]. The course of glycosylation in the presence of Ag_2CO_3 or Ag_2O in benzene at the boiling temperature is still unclear (modification due to *Meystre* and *Miescher*[26]). A characteristic feature shared by all reactions mentioned so far is that they proceed best in solvents of relatively low polarity.

Owing to the ready formation of the resonance-stabilized glycosyl cation [*(12)*—*(14)*] an S_N1 mechanism[***] has to be assumed for the solvolysis of haloses[16] and for glycosylation in the presence of soluble catalysts or acid acceptors[27–29]. It should be noted that bases or metal compounds added are not only acid acceptors; they can considerably enhance the rate of halogen release by a "push-pull" mechanism[30,31] in certain cases in cooperation with the solvent.

By analogy with the solvolysis schemes drawn up by *Winstein et al.*[32] and *Schleyer et al.*[24], the halose could react *via* an intimate ion pair *(12)*, a solvent-separated ion pair *(13)*, or a free ion *(14)*, depending upon the catalyst and solvent. In strongly nucleophilic solvents (ether, pyridine, *etc.*) the occurrence of oxonium [*e.g.* *(24)*] or ammonium ions [*e.g.* *(25)*] of type *(15)* with solvent participation can be expected.



(24)



(25)

That only the *trans* glycosides *(19)* are obtained in spite of the S_N1 mechanism could be explained in terms of a direct reaction between the alcohol and the intimate ion pair *(12)*[16]. Such ion pairs are known to react with nucleophiles with inversion[23,24,32,33]. However, an explanation of this kind is probably of restricted validity for 1-chloro sugars[34] since bromo haloses bearing nonparticipating substituents on C-2 have been shown to furnish mixtures of *cis*- and *trans* glycosides[35,36]. Accordingly, a neighboring group effect involving the 2-acyloxy group and C-1 must be responsible for the stereospecifity. This effect could consist in an interaction of the p orbitals of the carbonyl oxygen with the cation [as in *(18)*] or in formation of an acyloxonium ion *(17)*. Since no orthoesters *(20)* could be detected during the initial stages of the reaction[37] solvolyses appear to proceed *via* *(18)* owing to the large excess of nucleophile. In contrast, the usual glycosylation reactions with soluble catalysts should generally proceed *via* the acyloxonium ion *(17)*.

Studies on acyloxonium ions in general[38] and on the mode of reaction of transient acyloxonium ions *(17)* formed from sugar 1,2-orthoesters[39] have revealed that the ambidentate cations can, in principle, react in two different ways with an alcohol. Thus two possible reaction paths are open to *(17)*.

1) In neutral or alkaline solution a kinetically controlled reaction yields predominantly the orthoester *(20)*. With silver salicylate in tetrahydrofuran, for example this reaction is almost quantitative[40,41]. The acyloxonium ion *(17)*, and hence the orthoester *(20)*, are apparently formed particularly readily *via* an intermediate oxonium ion *(24)* of type *(15)*[42,43]. Orthoesters *(20)* can also be obtained from *cis* haloses in collidine[44] or in triethylamine[45], as well as in ethyl acetate on addition of $PbCO_3$[46]. While affording a simple preparation of orthoesters, this type of reaction frequently occurs as an undesired competing process in glycoside syntheses. This also applies to glycosylations in the presence of insoluble silver compounds. Pronounced orthoester formation is observed especially with sterically hindered alcohols whose concerted reaction to give the glycoside is too slow[40].

2) If the positive charge on the acyloxonium ion *(17)* is blocked by the anions of catalysts such as $AgClO_4$, pyridinium perchlorate, or soluble mercury salts in suitable solvents, the alcohol can attack at C-1 in a thermodynamically controlled

[*] A completely analogous scheme could be drawn for the C-2 epimeric sugars (*e.g.* D-mannose). In this case the *cis* haloses happen to be the more reactive compounds insofar as the halogen occupies an equatorial position.

[**] Here and in the following the traditional classification of mechanisms as S_N1 and S_N2 has been adopted [23, 24]. The occurrence of ion pairs in S_N2-type reactions as postulated by *Sneen* [25] has been disregarded. Reactions are formulated as proceeding *via* ion pairs only when their formation determines the rate of reaction.

[***] Solvolysis can also assume S_N2 character in nonpolar solvents with strong nucleophiles [16].

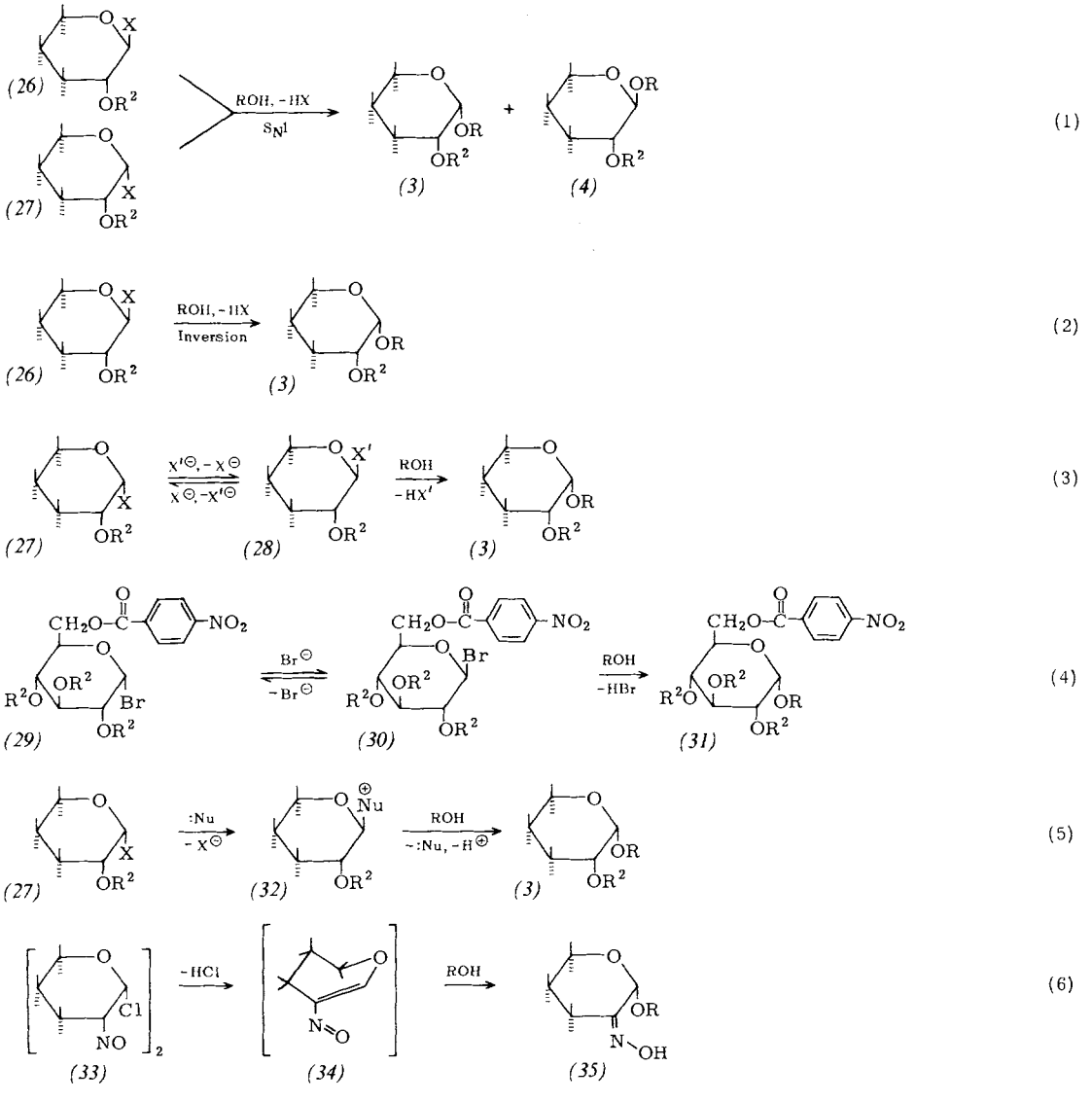
reaction yielding *trans* glycosides *(19)* stereospecifically. Elevated reaction temperatures favor formation of *(19)*[*].

The course of glycosylation described above is crucially based on the occurrence of acyloxonium ions. Although no definite proof for their formation has been obtained, the known reactions[38,39] of such ions provide a good explanation of the reaction course. Further evidence for the intermediacy of acyloxonium ions came from the occurrence of orthoesters, of orthoester-type by-products[48–50], and of by-products arising from orthoesters (or acyloxonium ions)[49,50], as well as the isolation of acyloxonium salts on reaction of *cis* haloses with $AgBF_4$[47]. Acyloxonium ions could be formed especially readily from *(14)* and *(15)* by nucleophilic attack of the carbonyl group on C-1, particularly since the acyloxonium ion is more stable than the glycosyl cation[47].

With highly polar solvents (acetonitrile, nitromethane) and catalysts having strongly complexing anions [$Hg(CN)_2$ or $HgBr_2$][51], however, no acyloxonium ion is apparently formed; instead the reaction proceeds *via* the glycosyl cation *(14)*. Reaction with the alcohol leads to a mixture of *cis* and *trans* glycoside [*(21)* and *(19)*] in a ratio depending on the structure of the sugar and the reaction conditions. This represents a possible method of obtaining *cis* glycosides after separation of anomers[51]. The reaction also occurs as an undesired side reaction in the preparation of *trans* glycosides, expecially in polar solvents.

trans Haloses *(23)*, *e.g.* *(6)*, *(7)*, and *(9)*, generally react with an alcohol in the presence of insoluble silver salts or bases by way of the intermediate acyloxonium ion *(17)* to give orthoesters *(20)*[20]. Small amounts of *cis* glycosides *(21)* are also formed by direct reaction. *trans*-1-Bromo-2-acylcyclohexanes behave similarly[52]. In accord with the reaction mechanisms postulated so far, attack by the alcohol on the acyloxonium ion can, however, also be directed towards C-1 by Lewis acids so that *trans* glycosides *(19)* are formed with retention.

Finally, the acyloxonium ion *(17)* has also been postulated as an intermediate in glycoside syntheses from sugar 1,2-orthoesters[39,46]. In this case *(17)* is formed by heating orthoesters *(22)* derived from simple alcohols (*e.g.* ethanol)



Scheme 2. Possibilities of systematic synthesis of *cis* glycosides.

[*] In the absence of other nucleophiles these acyloxonium ions can undergo intramolecular reaction with additional neighboring *trans* acyl groups, thus leading to rearrangement products [47].

with catalysts and can react with an added alcohol to give the *trans* glycoside [*(22)*→*(17)*→*(19)*]. Transesterification

[(22)→(17)→(20)] yielding the new orthoester (20) can occur as competing reaction. A further possible preparation of *trans* glycosides (19) consists in rearrangement of an orthoester formed by another route into the isomeric glycoside [(20)→(17)→(19)][39, 53] (see Section 5).

2.3. Preparation of *cis* Glycosides

For the reasons mentioned in the foregoing Section, peracylated haloses and orthoesters are of little value for the directed synthesis of *cis* glycosides. Syntheses of *cis* glycosides generally start from 1-halo sugars bearing a nonparticipating substituent on C-2. The resulting possibilities of systematically building up *cis* glycosides are summarized in Scheme 2.

In most cases, reactions of such haloses [(26) or (27)] under typical S_N1 conditions (*e.g.* solvolysis) [eq. (1)] lead to a mixture of *cis* and *trans* glycosides [(3) and (4)], irrespective of the anomeric configuration at C-1. The proportion of *cis* glycoside can be varied to a certain degree by changing the reaction conditions and the kind of alcohol; however, it is determined mainly by the structure of the halose.

The corresponding *trans* haloses (26) are more favorable for the preparation of *cis* glycosides, in combination with reaction conditions promoting an S_N2-type transition state or formation of intimate ion pairs [eq. (2)]. Nonpolar solvents and insoluble silver salts, or the use of 1-chloro compounds, are thus most conducive to *cis* glycoside formation. Owing to partial isomerization to the *cis* halide during reaction and a side reaction *via* glycosyl cations, this method can produce considerable quantities of *trans* glycosides.

A rather promising principle [eq. (3)] has been applied by *Lemieux*[54, 55]. In an equilibrium reaction with tetraethylammonium halide, a *cis* halose (27) is converted into the more reactive *trans* halose (28) which then rapidly reacts to give the *cis* glycoside (3). A similar principle could apply to the *cis* glycoside synthesis described by *Igarashi*[56] in which a *cis* halose bearing a benzyl substituent at C-2 is reacted with an alcohol in the presence of silver perchlorate and collidine. *Igarashi*[57] showed, however, that the relatively unstable *cis*-1-perchlorate results on reaction of a halose with $AgClO_4$ in the absence of alcohol. The exceptionally high yields of *cis* glycoside could however be better rationalized by initial formation of a *trans*-1-perchloric ester (28), $X' = ClO_4$, which rapidly isomerizes to the *cis* ester in the absence of alcohol, but is transformed much more rapidly into the *cis* glycoside when alcohol is present.

Surprisingly, certain substituents on C-6, C-4, and C-3 of the halose appear to exert a powerful influence on the stability of the *trans* haloses[30, 58, 49]. Thus a *p*-nitrobenzoyl group on C-6 apparently shifts the equilibrium between *cis* and *trans* haloses in the direction of the latter, thereby facilitating further fast reaction to give the *cis* glycoside[30, 34, 58] [see eq. (4)], whereas a *p*-methoxybenzoyl group as substituent on C-6 leads almost exclusively to the *trans* glycoside[34].

The fact that positively charged substituents on C-1 are most stable in the equatorial position—the so-called reverse anomeric effect[60]—opens up a further possibility for the formation of reactive *trans* compounds. *West* and *Schuerch*[61] treated *cis* haloses with a nucleophile (:Nu), *e.g.* with triethylamine, to give a *trans* onium compound (32) [cf. (25)] that reacts further with alcohols to form the *cis* glycosides [see eq. (5)].

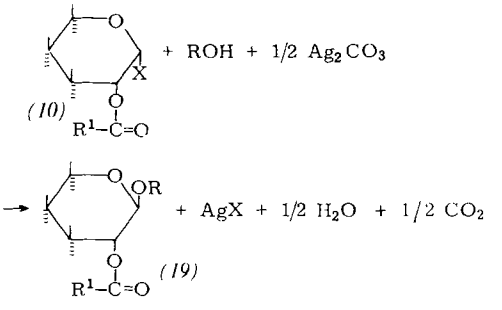
A completely different directing effect was exploited by *Lemieux*[62] for glycosylation with 2-nitroso *cis* haloses (33) [eq. (6)]. In dimethylformamide these haloses react *via* an intermediate nitrosoglycal (34) with stereospecific 1,4 addition of the alcohol to the diene system to give the *cis* glycoside (35) in high yield[63]. The *cis* glycosaminide or the *cis* glycoside can be obtained from this product (see Section 4.6).

3. Glycosides form 1-Haloses Having Participating Substituents on C-2

Since the successful studies by *Koenigs* and *Knorr*[64] dating from 1901, 1-halo sugars have been converted in large numbers into glycosides by treatment with alcohols under a variety of conditions. We shall now report a selection of recent results[*].

3.1. In the Presence of Insoluble Salts

In the original form of the Koenigs-Knorr synthesis, the halose was allowed to react with an alcohol in the presence of an insoluble silver compound, usually Ag_2O or Ag_2CO_3 (for a survey see ref.[65–67]). The water formed also reacts with



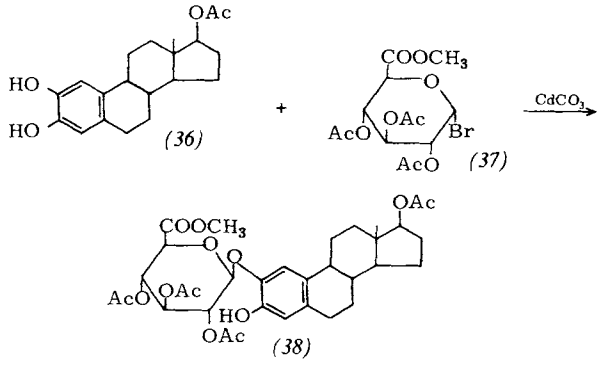
the halose and reduces the yield. This water is nowadays removed by the following principal methods:

1) An inorganic dessicant (*e.g.* drierite) is added to the reaction mixture and the process is performed at room temperature. This technique is frequently employed in the synthesis of oligosaccharides in which the halose (in chloroform or methylene chloride) is reacted with the alcohol in the presence of Ag_2CO_3, $CaSO_4$, and I_2 (examples[68–70]). Good results are obtained with primary alcohols. It is assumed that iodine suppresses the formation of orthoester-type by-products[48], probably by stabilization of a bimolecular transition state on Ag_2CO_3 leading to the glycoside[22].

2) The variant due to *Meystre* and *Mieschер*[26] has been extensively used, above all in the synthesis of steroidal glycosides: the resulting water is distilled off as an azeotrope with solvent benzene. Yields are moderate to good[26, 71, 72]; however, sensitive alcohols can lose water and undergo other changes[65]. *Conrow* and *Bernstein*[73] have demonstrated that the otherwise difficultly accessible glycosides of phenolic steroids can be readily obtained by use of $CdCO_3$ (in place of silver compounds) in boiling toluene. Even estrogens having a pyrochatechol structure [*e.g.* (36)], which are oxidized by silver compounds, can be converted into the glucuronide

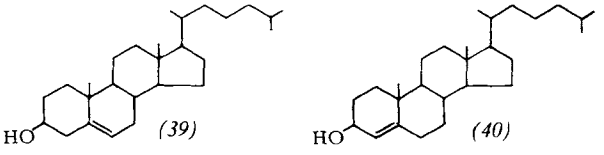
[*] No attempt at complete coverage of the literature has been made. Apart from methodological advances, a number of characteristic examples have been chosen from recent publications wherever possible.

(38) with glucuronyl halide *(37)* in toluene in the presence of this new catalyst[73a]. *trans*-Alkyl glycosides can also be conveniently prepared in the presence of HgO[74].



The yields of the above glycosylation reactions are often rather poor, particularly with secondary alcohols, and cannot be raised significantly by a large excess of halose. This is due to side reactions whose products can in turn also sometimes undergo glycosylation. Apart from the reaction with water, the main contenders are those leading to the orthoester *(20)*[40] and to products arising from the intermediate acyloxonium ion *(17)* (*e.g.* alkyl acetate, alkyl 3,4,6-tri-*O*-acetyl-α- and -β-glucopyranoside)[43, 49, 50]. In the absence of an alcohol, too, the halose reacts with Ag_2O or Ag_2CO_3 to give orthoester-type products[40, 43, 48, 50]; after reaching a given conversion, however, the reaction becomes very slow[40, 43]. The major reaction product, whose structure has yet to be elucidated, undergoes extremely ready conversion into a 2,3,4,6-tetra-*O*-acyl sugar on work-up of the reaction mixture[43, 50].

In our new glycosylation variant[21, 40] we react the halose with the alcohol in the presence of the silver salt of a hydroxy carboxylic acid (preferably 4-hydroxyvaleric acid) in diethyl ether as solvent. Considerable importance attaches to the nature of the solvent used. This method is particularly effective for glycosylation of steroidal alcohols [*e.g.* cholesterol *(39)* and tigogenin *(41)*][40] (see Table 3). Since no water has to be removed (the silver salt yields the free hydroxy carboxylic acid and AgHal) and the reaction proceeds at a considerable rate even at −10 °C, the method is also suitable for highly sensitive alcohols. Allyl alcohols of the steroid series [*e.g.* 4-cholesten-3-ol *(40)*], which usually lose water to form the corresponding diene (*e.g.* 3,5-cholestadiene), can be glycosylated by the above method[40]. Reaction in diethyl ether at low temperature is also favorable for Ag_2O; however, orthoesters are more readily formed with that catalyst[40].



A comparison of the yields obtained in the presence of various silver salts is informative with regard to the function of the silver compound in these reactions (see Table 1).

Surprisingly, the "classical" silver compounds Ag_2O and Ag_2CO_3 were found not to be the best reagents. Instead, apart from silver 4-hydroxyvalerate mentioned above, silver salts of other hydroxy carboxylic acids (especially salicylic

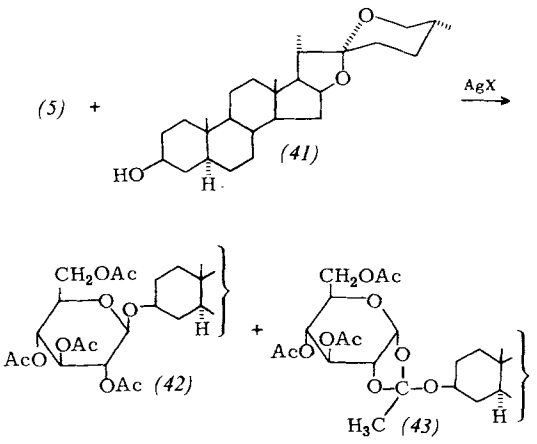
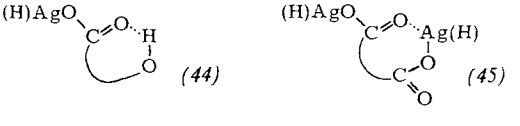


Table 1. Variation of the yield of glucoside *(42)* and orthoester *(43)* with the silver compound AgX. Reaction of tigogenin *(41)* with 2,3,4,6-tetra-*O*-acetyl-α-D-glucosyl bromide *(5)* in diethyl ether at 20 °C under standard conditions [40]. *n* = possible number of ring members in the silver compound.

AgX	Yield [%] *(42)*	*(43)*	*n*
C_2H_5—COOAg	24	—	—
Cl_3C—COOAg	25	—	—
$HOCH_2$—$(CH_2)_4$—COOAg	26	—	9
CH_3—CHOH—$(CH_2)_3$—COOAg	25	—	8
CH_3—CHOH—$(CH_2)_2$—COOAg	55 65 [a]	1 2	7
CH_3—CHOH—CH_2—COOAg	40	20	6
Silver salicylate	60 50 [a]	30 40	6
C_2H_5—COH(CH_3)—COOAg	41	—	5
Disilver maleate	55 [a]	5	7
Disilver malonate	40	20	6
Disilver oxalate	35	5	5
Ag_2CO_3	45	1	4
Ag_2O	50	5	—
$AgNO_3$	40	—	—

[a] At −10 °C.

acid)[75] and dicarboxylic acids (especially maleic acid) proved particularly favorable. A striking connection is observed between product formation and the distance between the two functional groups in the silver salt. In principle, both the carboxy group (with formation of 1-acyl glycoses) and the hydroxy group of the silver salt are capable of reaction with the sugar in place of the alcohol to be glycosylated[49, 76], and the salts of simple acids (propionic acid, trichloroacetic acid) as well as 6- and 5-hydroxy carboxylic acids do indeed preferentially form the 1-acyl glycoses. Possibly, the 4-, 3-, and 2-hydroxy carboxylic and 1,4-, 1,3-, and 1,2-dicarboxylic acids in solution and sometimes the corresponding silver salts in the crystalline state are capable of neighboring group participation between OH or OAg and the carbonyl group [*e.g.* in *(44)* and *(45)*] which lowers the extent of a nucleophilic attack by the acid anion on the sugar. The relationship between the yield and possible number of ring members is obvious[*].



A better understanding of this reaction has been sought in detailed studies of its stereochemistry[49] and kinetics[22]. The

[*] It is still unclear why silver salts whose anions can form a six-membered ring should be more prone to orthoester formation.

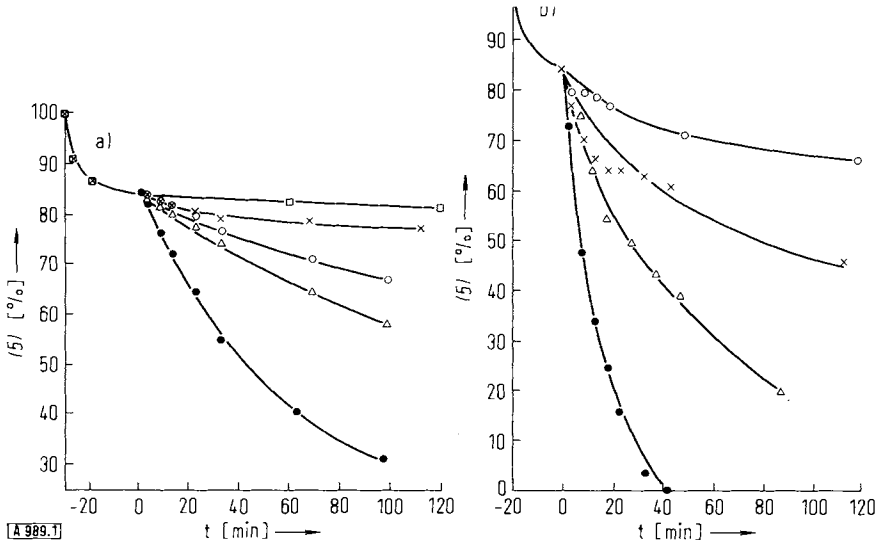
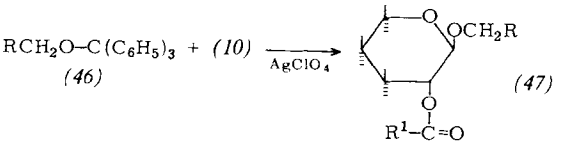


Fig. 1. a) Kinetics of the reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-glucosyl bromide *(5)* in diethyl ether at 0°C in the presence of Ag_2CO_3 with methanol (•, 1.07; ▵, 0.53; ○, 0.32; ×, 0.11; □, 0 equivalents of CH_3OH). b) As for Fig. 1a; however, reaction is carried out with equivalent amounts •, water; ▵, methanol; ×, isopropyl alcohol; ○, cholesterol *(39)*. Alcohols and water were added 30 and 20 min, respectively, after the initial reaction of Ag_2CO_3 and *(5)*. The amount of unreacted *(5)* is plotted [22].

reaction rate depends upon the amount and nature of the alcohol (see Fig. 1). Addition experiments with competing nucleophiles of different strengths, in which the rates and product patterns were compared, also clearly indicated that the rate-determining and product-determining steps of the reaction are identical. In contrast to solvolysis reactions of haloses and glycosylations in the presence of soluble catalysts, the alcohol here participates in the rate-determining step. The reaction itself can probably be best depicted as shown in *(11)*[22]. Significantly it can apparently only take place on the surface of an insoluble silver salt, the halose halogen first interacting with the silver. The actual reaction takes place owing to a "push-pull" effect only on addition of the alcohol. A certain resemblance can be detected between the postulated reaction course and the mechanism assumed by *Kornblum et al.*[77] for the reaction between alkyl halides and silver nitrate or nitrite.

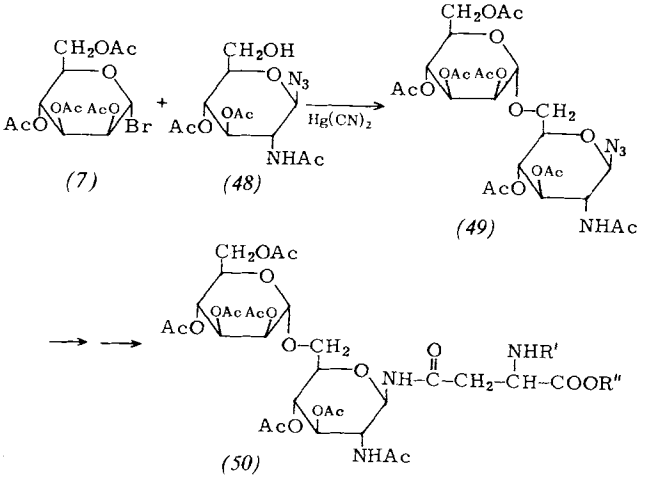
3.2. In the Presence of Soluble Catalysts

Increasing use is being made of soluble catalysts in the production of *trans* glycosides by the Koenigs-Knorr synthesis since they usually react faster, and some offer the advantage of working in homogeneous phase. $Hg(CN)_2$, $HgBr_2$, or $AgClO_4$ are preferentially used in oligosaccharide syntheses. Silver perchlorate has been used primarily in combination with Ag_2CO_3[78, 79] in order to raise the rate of reaction.



Reaction of haloses with trityl ethers *(46)* derived from the alcohols in the presence of $AgClO_4$ according to *Bredereck*[29] has also proved of value. The method affords good yields of *trans* glycosides *(47)* from primary alcohols[29, 80]. In both cases mentioned they probably first form the 1-perchlorate sugars[57, 81] which can rapidly react further to the acyloxonium ion *(17)*[29].

Of the mercury salts, which have now been employed for some time, most frequent use is nowadays made of $Hg(CN)_2$[83] introduced by *Helferich*[82]. Reaction is usually carried out in benzene/nitromethane as solvent since *trans* glycosides are then formed almost exclusively, while the *cis* glycoside can predominate in pure nitromethane[84, 85]. The method was extensively used, for example, by *Jeanloz et al.* (*e.g.*[86, 87]) for synthesizing oligosaccharides of biological interest. As an example we can consider the synthesis of a glycoprotein precursor in which the α-linked *trans* disaccharide *(49)* is formed from a glucosamine derivative *(48)* and 2,3,4,6-tetra-*O*-acetyl-α-D-mannosyl bromide *(7)* in 74% yield[86]. After reduction of the azide to the amino group in *(49)*, it is reacted with an aspartic acid derivative to give a structure of type *(50)* occurring in glycoproteins. Other schools have also conducted syntheses in the presence of $Hg(CN)_2$, mainly with the aim of producing oligosaccharides (see, *e.g.*, refs.[88–90]).



Problems arise in the preparation of oligosaccharides and glycosides in which 2-amino-2-deoxy sugars form the glycosidically bound component. Although neighboring group participation of the C-2 substituents in the respective haloses is possible during glycosylation (*e.g.* in 2-*N*-acetyl, 2-*N*-benzoyl, 2-*N*-benzyloxycarbonyl sugars), and the reaction therefore leads to *trans* glycosides[91], the yields are nevertheless low, since these haloses are relatively unstable and frequently also give rise to derivatives of oxazoline *(68)*[91a,92] or of oxazolidone[92].

As already mentioned, large amounts of *cis* glycosides are formed with $Hg(CN)_2$ in polar solvents[84,85]. A mixture of $Hg(CN)_2$ and $HgBr_2$, likewise introduced by *Helferich*[51,93], ensures even better yields of *cis* glycosides from glycosylations performed in polar solvents. The $HgBr_2$ formed anyway during the reaction accelerates dissociation of the haloses by complex formation (probably as $[HgBr_3]^-$)[93]. Isolation of the pure glycosides involves separation of the *cis/trans* glycoside mixture. Although the mixture rarely contains more than 50% of the *cis* glycoside this was until recently the best available synthesis of *cis* glycosides and was used primarily for preparing α-linked disaccharides[51,93,94]. Primary alcohols, however, usually afford *trans* glycosides[88,95], and use of the method with *trans* haloses, *e.g.* 2,3,4-tri-*O*-acetyl-α-L-rhamnosyl bromide *(9)*, leads to excellent yields of *trans* glycosides[96].

4. *cis* Glycosides from Haloses Having Nonparticipating Substituents on C-2

4.1. From *cis* or *trans* Haloses under Typical S_N1 Conditions

On reaction of haloses having nonparticipating substituents (the benzyl ether group is generally used in this case) with alcohols under typical S_N1 conditions, both the *cis* and the *trans* halose give the same ratio of *cis* and *trans* glycoside [see eq. (1)]. A number of syntheses starting from *trans* haloses included in Section 4.2 should conceivably be listed under the present heading since the corresponding *cis* halose might possibly give the same ratio of *cis* and *trans* glycoside. Thus *Austin et al.*[36] prepared mixtures of *cis*(α) and *trans*(β) glucosides and galactosides, from which both anomers could be obtained pure by reaction of the α and β chloride of 2,3,4,6-tetra-*O*-benzyl-D-glucose and -D-galactose. The method was later extended to other sugars[97]; however, the yields of *cis* glycoside are generally only moderate.

The 2,4-dinitroanilino[98], *p*-methoxybenzylideneamino[99], bis(phenoxy)phosphinylamino[92], dichloroacetylamino[100], and trifluoroacetylamino groups[101] have been used as functional groups on C-2 for haloses of 2-amino-2-deoxy sugars not displaying neighboring group effects. Here, too, glycosylation yields mixtures of *cis* and *trans* glycosides which have to be separated. The method is used with amino sugars to produce both *cis* and *trans* glycosaminides.

4.2. From *trans* Haloses with Inversion

It has long been established practice in the systematic construction of *cis* glycosides to start from *trans* haloses [see eq. (2)] whose substituents on C-2 are incapable of neighboring group participating (for earlier work, see refs.[1,6,9,10]).

Wolfrom et al.[102,103] used the nitric ester group on C-2, which however strongly deactivates the halogen on C-1. While fair yields are obtained with primary alcohols[102], they are much lower with secondary alcohols, particularly in disaccharide synthesis[103]. The chlorosulfate protecting group, readily introduced by acylation with SO_2Cl_2, has been used successfully in the preparation of α-D-xylosides[104], as has the 2,3-carbonyldioxy group in the preparation of β-D-mannosides[105]. The 2-trichloroacetoxy and 2-hydroxy group on C-2 are also very suitable as nonparticipating functional groups[106-108]. Detailed studies of glycosylation with 3,4,6-tri-*O*-acetyl-β-D-glucopyranosyl chloride and -β-D-galactopyranosyl chloride in benzene in the presence of mercury succinate[108,109] and in methylene chloride in the presence of silver carbonate/silver perchlorate[110] have been conducted by *Helferich* and *Müller*[108-110]. They obtained surprisingly good yields, especially of α-linked oligosaccharides of glucose and galactose (see Table 3).

4.3. By Previous Anomerization of the Halose

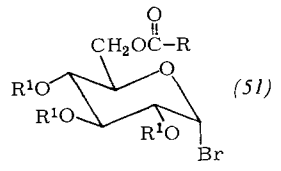
Lemieux, Hendriks, et al.[54,55] introduced the halogen-ion catalyzed reaction of *cis* haloses for the synthesis of *cis* glycosides (see eq. (3)). They treated perbenzylated *cis* haloses of D-glucose[54], D-galactose[110a], or L-fucose[110b] with alcohols in the presence of tetraethylammonium bromide and ethyldiisopropylamine (Hünig base). In methylene chloride as solvent (in some cases with addition of dimethylformamide) they obtained remarkably good yields of *cis* glycosides (see Table 3). With substituents prone to acyl migration in the alcohol component the Hünig base could be replaced by a molecular sieve[111b]. Apart from disaccharides this method has already yielded two trisaccharides which function as components of blood-group active oligosaccharides[110a,b].

Igarashi et al.[56] studied the reaction of *cis* haloses with alcohols in the presence of silver perchlorate and *sym*-collidine in several solvents: By varying the reaction conditions they found an exceptionally specific synthesis of *cis* glycosides in diethyl ether as solvent, and obtained a variety of α-linked disaccharides consisting of two molecules of D-glucose in very good yields (see Table 3).

This procedure represents a logical development of the reaction described by *Hasegawa et al.*[111] which is conducted in the presence of Ag_2CO_3 and $AgClO_4$ in chloroform (benzene) with 10—20% dioxane, and also affords *cis* glycosides, admittedly in not such good yields.

4.4. Steric Control of Glycosylation by Substituents on the Halose

It has recently been found that certain substituents on C-6, C-4, and C-3 of the halose have a pronounced effect on the steric course of the reaction, thus providing a means of stereochemical control [see eq. (4)]. Following initial observations by *Ishikawa* and *Fletcher*[58] on 6-*p*-nitrobenzoyl haloses, which yield mainly *cis* glycosides on solvolysis, *Fréchet* and *Schuerch*[34] undertook systematic studies on the effect of the substituent on C-6 of haloses *(51)* upon the *cis/trans* ratio of the glycosides produced on solvolysis (see Table 2). They found a striking dependence of the *cis/trans* ratio of the resulting methyl glycosides upon the substituent on C-6[34];



(51)

$R^1 = CH_2-C_6H_5$

Table 2. Methanolysis of *(51)* to *trans*(β) and *cis*(α) methyl glycoside [34].

R	*trans*:*cis*
p-CH_3O—C_6H_4	93:7
C_6H_5	84:16
3,5-$(NO_2)_2$—C_6H_5	75:25
CH_3	65:35
p-NO_2—C_6H_4	8:92

however, this ratio is strongly dependent upon the concentration of the alcohol and the reaction conditions[30]. *Flowers et al.*[59, 112] were then able to show for fucose derivatives that a substituent on C-3 and C-4 also influences the steric course of glycosylation.

The corresponding 1-chloro compounds usually react with extensive inversion (presumably owing to intimate ion pair formation)[34]. In contrast to the foregoing descriptions we also observed consistent inversion on reaction of the bromides in the presence of insoluble silver salts under S_N2 conditions, regardless of the substituent on C-6[49].

Meanwhile the utility of the new method has been established for the synthesis of α-linked steroidal glycosides[113] and oligosaccharides[59, 114, 115] (see Table 3).

4.5. Exploitation of the Reverse Anomeric Effect

West and *Schuerch*[61] treated *cis* haloses with a powerful nucleophile (triethylamine, dimethyl sulfide, or triphenylphosphane) which can only react with the halose to form an onium compound [see eq. (5)]. These reactive intermediates then react with alcohol to give the *cis* glycoside almost exclusively. The scope of this promising method has not yet been published.

4.6. From 2-Nitroso Haloses

Unlike the substituents on C-2 considered so far, the nitroso group exerts a *cis*-directing action on glycosylation. This fact constitutes the basis of an effective *cis* glycoside synthesis developed by *Lemieux, Nagabhushan, et al.*[116]

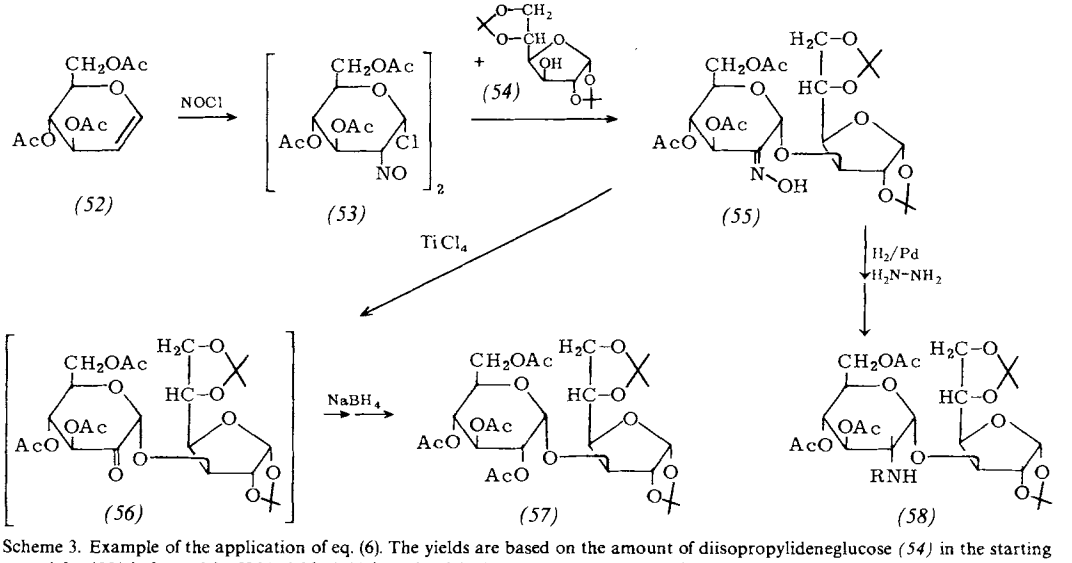
Nitroso sugars of type *(33)* [cf. eq. (6)] are easily obtained from the readily accessible acetylated glycals [*e.g.* glucal *(52)*] by *cis* addition of nitrosyl chloride to give *(53)*[117]. These compounds crystallize as dimers. Glycosylation of alcohols is best carried out in dimethylformamide at room temperature without addition of an acid acceptor. The complicated equilibria established on dissolution of *(53)* in DMF have been thoroughly studied, both in the absence[118] and in the presence of alcohol[63].

Condensation with an alcohol gives good yields, even in the case of complex sugar derivatives such as 1,2:5,6-diisopropylidene-α-D-glucofuranose *(54)* which is usually difficult to glycosylate.

The content of *trans* glycoside is generally low; in one case, however, 8.7% of *trans* product was obtained[63], and in another, under different conditions, the *trans* glycoside even predominated[119].

Deoximation is best performed with acetaldehyde/HCl or $TiCl_4$[120]. The keto sugars *(56)* can be isolated in high yields, but are usually reduced directly. In syntheses starting from glucal, the reaction with $NaBH_4$ or B_2H_6 is rather stereoselective. Only 4% of α-D-mannosido derivative accompany 96% of the α-D-glucosido derivative *(57)*[55]. In contrast, syntheses starting from galactal give comparable yields of the α-D-galactosido and α-D-talosido compounds. The same applies to the direct reduction of the oximino glycosides, which is stereoselective, giving more than 90% of the α-D-glucosamido compound [*e.g. (58)*], only in the case of glucal[121] (Scheme 3).

The above method is well suited to the preparation of *cis* glycosides[55, 116] and *cis* glycosaminides[116, 121]. It is, however, rather involved and separation of by-products can present problems. A favorable application lies in the introduction of α-linked D-glucosaminide[116, 121] and D-glucoside groups[55, 116] which are abundant in Nature (see Table 3).

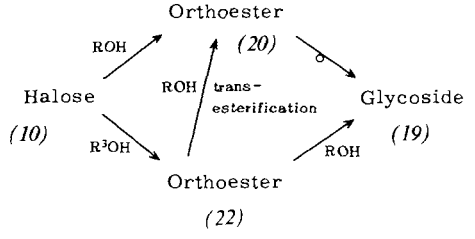


Scheme 3. Example of the application of eq. (6). The yields are based on the amount of diisopropylideneglucose *(54)* in the starting materials. *(55)* is formed in 59% yield, *(58)* in 52% yield (+ <5% α-D-mannosamine derivative), *(57)* in 43% yield (+*ca.* 1.5% α-D-mannose derivative).

5. Glycosides from Orthoesters

Of the methods available for preparation of *trans* glycosides *(19)*, the route proceeding *via* the orthoesters *(22)* has become increasingly significant during the past decade. In addition to other schools, *Kochetkov et al.*[39, 46, 53, 122] have played a leading role in the systematic study and application of the orthoester method (for a detailed review, see ref.[39]).

Starting from a halose *(10)*, the initial step consists in preparing the orthoester *(22)* of a simple alcohol R^3OH, which is then reacted with the more complex alcohol ROH to form the glycoside *(19)*. Alternatively the orthoester *(20)* of the



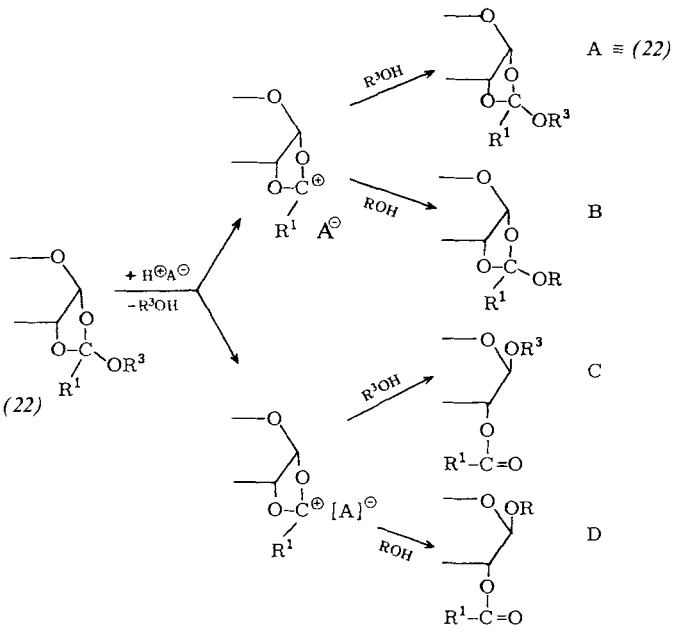
ROH = alcohol to be glycosylated
R^3OH = methanol, ethanol, or *tert*-butyl alcohol

complex alcohol may be prepared[41, 53, 123] and then rearranged to the glycoside[53, 124].

Preparation of the orthoesters closely resembles the Koenigs-Knorr synthesis: the starting materials are an acylated halose, an alcohol and a halogen-binding additive. *trans* Haloses *(23)* yield the orthoester directly in neutral or basic solution[125]. Unter certain conditions the more readily accessible *cis* haloses *(10)* can also be used. Orthoesters [*(20)*, *(22)*] are best obtained from *cis* halose in the presence of a strongly nucleophilic solvent which cannot form strong bonds but merely an oxonium *(24)* or ammonium ion *(25)*. The orthoester *(20)* is then readily formed *via* the acyloxonium ion *(17)*. For instance, orthoesters are formed from *cis* haloses and an alcohol with collidine[44], with $PbCO_3$ in acetic ester[46], and with silver salicylate in tetrahydrofuran[41]. The last-named method[41] provides almost quantitative yields of the orthoesters of highly complex alcohols. Kinetic studies and examination of by-products have shown the reaction to proceed with participation of solvent tetrahydrofuran [*(10)*→*(24)*→*(17)*→*(20)*][42]. Reaction of *cis* haloses with an alcohol in the presence of tetrabutylammonium bromide is especially suited to the preparation of orthoesters, too, intermediate anomerization yielding the *trans* halose[45]. A primary anomerization to the β-nitrate is also involved in the reaction of *cis* haloses with alcohols in the presence of silver nitrate. The β-nitrate reacts further *via* the acyloxonium ion intermediate, furnishing the orthoester[126].

A characteristic feature of sugar orthoesters is their sensitivity towards acids, which leads to their hydrolysis in aqueous solution. On rigorous exclusion of water the orthoester can be made to yield the glycoside with an alcohol ROH in the presence of catalytic amounts of acid or Lewis acid. In principle, the products A—D may be expected.

The orthoesters A and B are formed by transesterification, where A ≡ *(22)* (starting material). D is the desired glycoside, C the glycoside of the more simple alcohol. Choice of the reaction conditions provides a large measure of control of products. Formation of A and C is usually suppressed by starting from orthoesters of lower alcohols which can readily

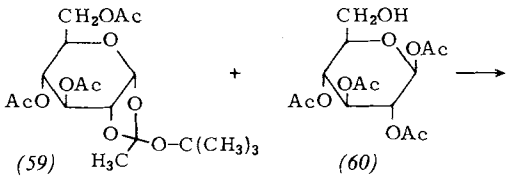


be distilled off during the reaction, or by chosing a group such as *tert*-butyl[53] whose recombination is largely precluded for steric reasons so that the added alcohol is more likely to become bonded to the sugar. Although it gives very good yields, glycosylation with *tert*-butyl orthoesters suffers from the instability of these compounds and the consequent impairment of reproducibility.

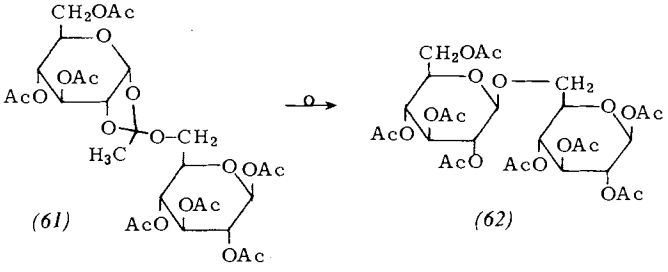
Whether orthoester or glycoside is formed depends upon the ratio of catalyst to orthoester, *i.e.* the critical ratio[39]. Glycosylation (C, D) predominates above the critical ratio, and transesterification (A, B) below. Consideration of the reaction scheme reveals that at high catalyst concentrations ($H^{\oplus}A^{\ominus}$) its anion can mask the positive charge of the acyloxonium, thus hindering nucleophilic attack of ROH which then takes place at the glycoside C-1. At low $A^{\ominus}$ concentrations direct attack and fresh orthoester formation becomes more likely[39]. However, at higher catalyst concentrations the formation of other by-products, such as the acetate ROAc[127, 128] and the dialkyl ether ROR[128, 129], becomes very pronounced. *cis* and *trans* 3,4,6-Tri-*O*-acylglycosides can also result[130, 131].

Each solvent-catalyst combination has a characteristic critical value. In polar solvents, like nitromethane, $HgCl_2$ and $HgBr_2$ are examples of suitable catalysts, whereas in nonpolar solvents, like chlorobenzene and dichloroethane, the perchlorates of pyridine and lutidine represent a better choice. The last-named combinations actually give the best yields.

The orthoester method has been successfully applied to numerous glycoside syntheses. Apart from glycosides of simple alcohols, those of *e. g.* hydroxy amino acids[53, 123], of steroidal and triterpenoidal alcohols[46, 127, 128], of glycerol derivatives[132], and, above all, of saccharides[39, 46, 53, 122] have also been prepared. The main strength of the method lies in the synthesis of di- and oligo-saccharides. A two-step synthesis of peracetyl gentiobiose *(62)* warrants mention as an example[53] (see also Table 3).



(59) (60)

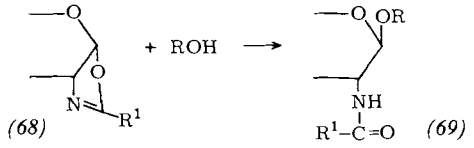


(61) (62)

Polysaccharides can also be built up relatively easily by the orthoester method[5, 13, 39, 133]. One possible route is to start from 1,2-orthoester derivatives bearing a free hydroxy group: polycondensation analogous to the disaccharide synthesis furnishes polysaccharides. A particularly elegant strategy, however, utilizes polymerization of tricyclic orthoesters [*e.g. (63)*] since no alcohol has to be eliminated. The sole requirement is an initiator alcohol which attacks the glycosidic C-1 atom of the sugar after acid-catalyzed ring cleavage to give *(65)* which can then be glycosylated to *(66)*. Frequent repetition of the process results in polymerization to form a linear polysaccharide *(67)* as shown for the synthesis of arabinan[133].

One disadvantage of the method is that electrophilic attack by $H^{\oplus}$ can also take place at the oxygen of C-2, resulting in 1→2 linked arabinose moieties in addition to 1→5 linked units. The arabinan obtained in 20% overall yield in the above example contains 92% of 1→5 linkages and 8% of 1→2 linkages[133]. With tricyclic xylose orthoesters, anhydride formation may occur instead of condensation[134].

As shown by *Micheel et al.*[135], and subsequently also by other authors[136, 137], oxazoline derivatives *(68)* of 2-amino-2-deoxy sugars frequently provide a very good entry into the *trans* glycosaminides *(69)* by a reaction resembling that of the orthoesters.



(68) (69)

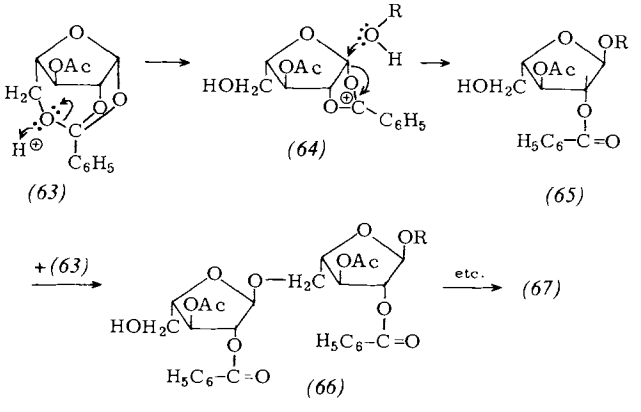
6. Outlook

The yields obtained on glucosylation of four alcohols by various methods are listed in Table 3[*]. The tabulated data clearly show the striking advances inherent in precisely those methods which have been developed in the last few years. Astonishingly enough, the preparation of *cis* glycosides now appears to be just as practicable as that of their *trans* counterparts, although it should be borne in mind that the starting materials for their synthesis are usually far less readily accessible. However, just a few years ago direct preparation of *e.g. cis*-linked disaccharides gave very poor yields; they were in fact usually obtained by isomerizing *trans* glycoside [138].

Table 3. Comparison of the yields obtained in the glucosylation of the four alcohols cholesterol *(39)*, 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose *(60)*, 1,2:3,4-diisopropylidene-α-D-galactopyranose *(70)*, and 1,2:5,6-diisopropylidene-α-D-glucofuranose *(54)* by various procedures. The yields are based on the alcohol used.

trans Glycosides (β-Glycosides)	*(39)* [%]	*(60)* [%]		*(70)* [%]		*(54)* [%]	
	[a]	[a]	[b]	[a]	[b]	[a]	[b]
Ag_2O, Ag_2CO_3 at RT with drying agent	33 [139]	74 [140]	64 [140]	41 [141]			10 [142]
with draing agent	55 [40]				—	—	
Ag_2O, Ag_2CO_3 at boiling temp.	43 [26]	—	—	—	—	—	—
Ag-4-hydroxyvalerate in ether at low temp.	58 [40]	—	—	—	—	—	—
Hg $(CN)_2$	26 [143]	—	—	—	21 [88]	—	—
$AgClO_4$, alcohol as trityl ether	—	58 [29]	—	25 [29]	—	—	—
with ethyl orthoester	45 [46]	61 [53] [c]	—	52 [46]	43 [46]	28 [46]	—
with *tert*-butyl orthoester	61 [53]	75 [53] [c]	—	—	—	46 [53]	28 [53]
cis-Glycosides [α-Glycosides]							
From *trans* haloses [eq. (2)]	29 [107]	25 [102]	50 [145]	68 [110]	66 [110]	—	1.8 [146]
	51 [144] [d]	63 [110]	61 [110]	—	54 [109]	—	37 [110]
Anomerization [eq. (3)]	—	75 [56]	—	65 [54]	—	42 [54]	—
						57 [56]	
Substituent effect of C-6 [eq. (4)]	—	—	—	63 [114]	—	—	—
From 2-nitroso sugars [eq. (6)]	37 [116] [e]	—	—	—	36 [55]	43 [55] [e]	23 [55]

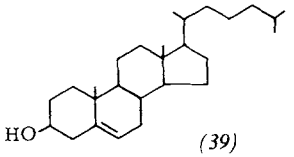
[a] Yield with protecting groups.
[b] Yield without protecting groups.
[c] Two-step procedure.
[d] Yield based on the glycosylation component.
[e] Yield based on the glucoside (without NO) with protecting groups.



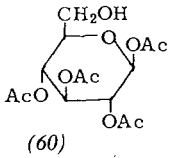
(63) (64) (65) (66) (67)

[*] Owing to the varying time requirements (*inter alia* for the preparation of the glycosylation components), the varying purity of the final products, and the difficult reproducibility of some syntheses, the reporting of product yields can be problematic. Nevertheless, we consider that the numerical data do give a general idea of the performance of the methods.

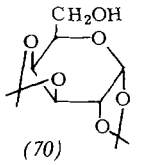
Only time will show whether, and to what extent, some of the very young methods[54-56,61,109,114] prove of value in other cases too.



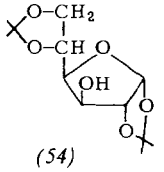
(39)



(60)



(70)



(54)

In spite of this progress, the syntheses of extended oligosaccharides still remain problematic. Perhaps syntheses on insoluble polymers, akin to *Merrifield*'s proven method for oligopeptides[147], could result in substantial improvements. The construction of relatively long oligosaccharide sequences by this method requires a series of protecting groups of various reactivities. The first member of the chain must be bound so firmly to the polymer *via* an anchoring group that subsequent removal of protecting groups and glycosylation steps are unable to sever the linkage. On completion of the syntheses, however, this group should be removable under conditions which do not modify the oligosaccharide chain. So far the allyl alcohol group (cleaved by ozone)[148], the nitrobenzyl- and nitroveratryl alcohol groups (cleaved photochemically)[149,150], and the carboxylic and sulfonic ester groups (cleaved by alkalis)[151,152] have been used for this purpose.

Apart from "persistent" protection of sugar hydroxy groups the hydroxy group required for subsequent glycosylation must only be temporarily protected and easily deblocked. The choice of blocking agent is largely determined by the other groups present. β-Benzoylpropionyl (removed with cyclization by hydrazine)[153], chloroacetyl (removed by thiourea)[154], *p*-nitrobenzoyl (removed by alkali)[155], and 1-thioglycoside (removed by Hg-salts)[156] show promise as protecting groups.

The main difficulty encountered in glycoside synthesis on polymers comes from the failure of any known glycosylation reaction to give even approximately quantitative yields. The number of error sequences will thus rise rapidly with increasing chain length. In spite of initial successes in the synthesis of di- and trisaccharides[148,150-152,155,157], application of this technique, and also of the systematic synthesis of higher oligosaccharides by other methods, will have to wait until the yields in the actual coupling step have been substantially increased. The numerous side reactions and resulting by-products thwart attempts to increase yields by use of a large excess of glycosylation reagent.

Future work in the field will therefore probably proceed on two fronts. One will be concerned with further optimization of known synthetic principles; precise mechanistic knowledge of the various glycosylation reactions and the attendant side reactions could greatly facilitate this work. The other will require a constant lookout for novel linking reactions, since the scope for improvement of existing methods appears to be limited.

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[1] Review: *R. J. Ferrier*, Fortschr. Chem. Forsch. *14*, 389 (1970).

[2] *R. U. Lemieux* and *S. Levine*, Can. J. Chem. *42*, 1473 (1964); *R. J. Ferrier, N. Prasad*, and *G. H. Sankey*, J. Chem. Soc. *C 1969*, 587; *G. Alfredsson* and *P. J. Garegg*, Acta Chem. Scand. *27*, 556 (1973).

[3] *M. Kuhn* and *A. v. Wartburg*, Helv. Chim. Acta *51*, 1631 (1968).

[4] *S. Inaba, M. Yamada, T. Yoshino*, and *Y. Ishido*, J. Amer. Chem. Soc. *95*, 2062 (1973).

[5] *C. Schuerch*, Accounts Chem. Res. *6*, 184 (1973).

[6] *J. Staněk, M. Černý, J. Kocourek*, and *J. Pacák*: The Monosaccharides. Academic Press, New York 1963, pp. 255ff.

[7] *W. G. Overend* in *W. Pigman* and *D. Horton*: The Carbohydrates. 3rd Edit. Academic Press, New York 1970, p. 279.

[7a] *R. J. Ferrier, R. W. Hay*, and *N. Vethaviyasar*, Carbohyd. Res. *27*, 55 (1973).

[8] *L. Hough* and *A. C. Richardson* in *S. Coffey*: Rodd's Chemistry of Carbon Compounds. Elsevier, Amsterdam 1967, Vol. I, Part F, pp. 327ff.

[9] *J. Conchie, G. A. Levvy*, and *C. A. Marsh*, Advan. Carbohyd. Chem. *12*, 157 (1957).

[10] *J. Staněk, M. Černý*, and *J. Pacák*: The Oligosaccharides. Academic Press, New York 1965, pp. 60ff.

[11] *R. J. Ferrier, R. D. Guthrie*, and *T. D. Inch*, Carbohyd. Chem. *1970*, 1; *J. S. Brimacombe, R. J. Ferrier, R. D. Guthrie*, and *T. D. Inch, ibid. 4*, 1 (1971); *5*, 1 (1972).

[12] *N. K. Kochetkov, O. S. Chizhov*, and *A. I. Bochkov*, MTP Int. Rev. Sci.-Org. Chem., Ser. One 7, 147 (1973).

[13] *N. K. Kochetkov*, Pure Appl. Chem. *33*, 53 (1973).

[14] A good review of knowledge accrued up to 1954 and a very stimulating application of recent theoretical concepts to glycosylation reactions is given by *R. U. Lemieux* [15].

[15] *R. U. Lemieux*, Advan. Carbohyd. Chem. *9*, 1 (1954).

[16] Review: *B. Capon*, Chem. Rev. *69*, 407 (1969).

[17] *L. J. Haynes* and *F. H. Newth*, Advan. Carbohyd. Chem. *10*, 207 (1955).

[18] *P. L. Durette* and *D. Horton*, Advan. Carbohyd. Chem. *26*, 49 (1971).

[19] *E. L. Eliel*, Angew. Chem. *84*, 779 (1972); Angew. Chem. internat. Edit. *11*, 739 (1972); *S. David, O. Eisenstein, W. J. Hehre, L. Salem*, and *R. Hoffmann*, J. Amer. Chem. Soc. *95*, 3806 (1973).

[20] *H. S. Isbell* and *H. L. Frush*, J. Res. Nat. Bur. Standards *43*, 161 (1949).

[21] *G. Wulff, G. Röhle*, and *W. Krüger*, Angew. Chem. *82*, 480 (1970); Angew. Chem. internat. Edit. *9*, 455 (1970).

[22] *G. Wulff* and *G. Röhle*, Chem. Ber. *105*, 1122 (1972).

[23] *C. K. Ingold*: Structure and Mechanism in Organic Chemistry. Cornell Univ. Press, Ithaca, N. Y. 1969.

[24] *D. J. Raber, J. M. Harris, R. E. Hall*, and *P. v. R. Schleyer*, J. Amer. Chem. Soc. *93*, 4821 (1971).

[25] *R. A. Sneen* and *J. W. Larsen*, J. Amer. Chem. Soc. *91*, 362 (1969); *R. A. Sneen* and *H. M. Robbins, ibid. 94*, 7868 (1972).

[26] *C. Meystre* and *K. Miescher*, Helv. Chim. Acta *27*, 231 (1944).

[27] *B. Lindberg*, Acta Chem. Scand. *1*, 710 (1947).

[28] *G. L. Mattok* and *G. O. Phillips*, J. Chem. Soc. *1958*, 130.

[29] *H. Bredereck, A. Wagner, D. Geissel, P. Gross, U. Hutten*, and *H. Ott*, Chem. Ber. *95*, 3056 (1962), and earlier works.

[30] *F. J. Kronzer* and *C. Schuerch*, Carbohyd. Res. *27*, 379 (1973).

[31] *Y. Pocker* and *D. N. Kevill*, J. Amer. Chem. Soc. *87*, 4760, 4771, 4778, 5060 (1965).

[32] *A. F. Diaz, I. Lazdins*, and *S. Winstein*, J. Amer. Chem. Soc. *90*, 1904 (1968).

[33] *A. Streitwieser, T. D. Walsh*, and *J. R. Wolfe*, J. Amer. Chem. Soc. *87*, 3682 (1965).

[34] *J. M. Fréchet* and *C. Schuerch*, J. Amer. Chem. Soc. *94*, 604 (1972).

[35] *A. J. Rhind-Tutt* and *C. A. Vernon*, J. Chem. Soc. *1960*, 4637.

[36] *P. W. Austin, F. E. Hardy, J. G. Buchanan*, and *J. Baddiley*, J. Chem. Soc. *1964*, 2128; *1965*, 1419.

[37] *G. Wulff* and *W. Schmidt*, unpublished.

[38] *S. Hünig*, Angew. Chem. *76*, 400 (1964); Angew. Chem. internat. Edit. *3*, 548 (1964).

[39] *N. K. Kochetkov* and *A. F. Bochkov* in *R. Bognár, V. Bruckner*, and *Cs. Szántay*: Recent Developments in the Chemistry of Natural Carbon Compounds. Akadémiai Kiadó, Budapest 1971, Vol. IV, p. 77.

[40] *G. Wulff, G. Röhle*, and *W. Krüger*, Chem. Ber. *105*, 1097 (1972).

[41] *G. Wulff* and *W. Krüger*, Carbohyd. Res. *19*, 139 (1971).

[42] *G. Wulff, W. Schmidt*, and *W. Krüger*, to be published.

[43] *G. Wulff*, Cron. Chim. (Milano), in press.

[44] *B. Helferich* and *K. Weis*, Chem. Ber. *89*, 314 (1956).

[45] *R. U. Lemieux* and *A. R. Morgan*, Can. J. Chem. *43*, 2199 (1965).

[46] *N. K. Kochetkov, A. Ya. Khorlin*, and *A. F. Bochkov*, Tetrahedron *23*, 693 (1967).

[47] *H. Paulsen*, Advan. Carbohyd. Chem. *26*, 127 (1971).

[48] *H. R. Goldschmid* and *A. S. Perlin*, Can. J. Chem. *39*, 2025 (1961).

[49] *G. Wulff, G. Röhle*, and *U. Schmidt*, Chem. Ber. *105*, 1111 (1972).

[50] *G. Wulff* and *W. Schmidt*; VI. Internat. Symposium on Carbohydrate Chemistry. Madison, USA, August 1972. Abstracts p. 57.

[51] *B. Helferich* and *J. Zirner*, Chem. Ber. *95*, 2604 (1962).

[52] *S. Winstein* and *R. E. Buckles*, J. Amer. Chem. Soc. *64*, 2780 (1942).

[53] *N. K. Kochetkov, A. F. Bochkov, T. A. Sokolovskaya*, and *V. J. Snyatkova*, Carbohyd. Res. *16*, 17 (1971).

[54] *K. B. Hendriks*, Ph. D. Thesis, Department of Chemistry, University of Alberta 1971; cited in [55]; *R. U. Lemieux, K. B. Hendriks*, and *K. James*, J. Amer. Chem. Soc. in press; *R. U. Lemieux* and *R. V. Sick*, *ibid*, in press.

[55] *R. U. Lemieux, K. James*, and *T. L. Nagabhushan*, Can. J. Chem. *51*, 42 (1973).

[56] *K. Igarashi, I. Irisawa*, and *T. Honma*, VI. Internat. Symposium on Carbohydrate Chemistry, Madison (USA), August 1972, Abstracts p. 56.

[57] *K. Igarashi, T. Honma*, and *J. Irisawa*, Carbohyd. Res. *15*, 329 (1970).

[58] *T. Ishikawa* and *H. G. Fletcher*, J. Org. Chem. *34*, 563 (1969).

[59] *M. Dejter-Juszynski* and *H. M. Flowers*, Carbohyd. Res. *28*, 61 (1973).

[60] *R. U. Lemieux* and *A. R. Morgan*, J. Amer. Chem. Soc. *85*, 1889 (1963).

[61] *A. C. West* and *C. Schuerch*, J. Amer. Chem. Soc. *95*, 1333 (1973).

[62] *R. U. Lemieux, S. W. Gunner*, and *T. L. Nagabhushan*, Tetrahedron Lett. *1965*, 2149.

[63] *R. U. Lemieux, Y. Ito, K. James*, and *T. L. Nagabhushan*, Can. J. Chem. *51*, 7 (1973).

[64] *W. Koenigs* and *E. Knorr*, Ber. Deut. Chem. Ges. *34*, 957 (1901).

[65] *W. W. Zorbach* and *K. V. Bhat*, Advan. Carbohyd. Chem. *21*, 273 (1966).

[66] *S. Bernstein, J. P. Duzza*, and *J. P. Joseph* in *S. Bernstein* and *S. Salomon*: Chemical and Biological Aspects of Steroid Conjugation. Springer, Berlin 1970, p. 1.

[67] *W. L. Evans, D. D. Reynolds*, and *E. A. Talley*, Advan. Carbohyd. Chem. *6*, 27 (1951).

[68] *D. D. Reynolds* and *W. L. Evans*, J. Amer. Chem. Soc. *60*, 2559 (1938).

[69] *P. A. J. Gorin* and *A. S. Perlin*, Can. J. Chem. *39*, 2474 (1961).

[70] *J. M. Berry* and *G. G. S. Dutton*, Can. J. Chem. *50*, 1424 (1972).

[71] *W. W. Zorbach, S. L. DeBernardo*, and *K. V. Bhat*, Carbohyd. Res. *11*, 567 (1969).

[72] *J. J. Schneider*, Carbohyd. Res. *17*, 199 (1971).

[73] *R. B. Conrow* and *S. Bernstein*, J. Org. Chem. *36*, 863 (1971).

[73a] *G. Röhle* and *H. Breuer*, Hoppe-Seylers Z. Physiol. Chem., in press.

[74] *L. R. Schroeder* and *J. W. Green*, J. Chem. Soc. *C 1966*, 530.

[75] The effectiveness of silver salicylate has meanwhile been confirmed elsewhere: *A. Ya. Veinberg, G. J. Roslovtseva*, and *G. J. Samokhvalov*, Zh. Obshch. Khim. *43*, 688 (1973); Chem. Abstr. *79*, 32349 (1973). Silver succinate is also suitable for the same purpose: *B. Helferich* and *W. M. Müller*, Chem. Ber. *103*, 3350 (1970).

[76] *G. Wulff, W. Krüger*, and *G. Röhle*, Chem. Ber. *104*, 1387 (1971).

[77] *N. Kornblum, W. J. Jones*, and *D. E. Hardies*, J. Amer. Chem. Soc. *88*, 1704, 1707 (1966).

[78] *M. L. Wolfrom, A. O. Pittet*, and *I. C. Gillam*, Proc. Nat. Acad. Sci. USA *47*, 700 (1961).

[79] *L. P. Egan, J. R. Vercelotti*, and *W. T. Lowry*, Carbohyd. Res. *23*, 261 (1972).

[80] *J. Lönngren* and *S. Svensson*, Acta Chem. Scand. *25*, 1155 (1971).

[81] *Yu. A. Zhdanov, G. A. Korolchenko, G. N. Dorofeenko*, and *G. I. Zhungietu*, Dokl. Akad. Nauk SSSR *154*, 861 (1964); Chem. Abstr. *60*, 14596 (1964).

[82] *B. Helferich* and *K. F. Wedemeyer*, Liebigs Ann. Chem. *563*, 139 (1949).

[83] Review: *H. M. Flowers*, Methods Carbohyd. Chem. *6*, 474 (1972).

[84] *K. Matsuda* and *T. Sekiguchi*, Nippon Nogei Kagaku Kaishi *33*, 309 (1959); Chem. Abstr. *58*, 5774 (1963).

[85] *J. Lehmann* and *D. Beck*, Liebigs Ann. Chem. *630*, 56 (1960).

[86] *M. A. E. Shaban* and *R. W. Jeanloz*, Carbohyd. Res. *23*, 243 (1972).

[87] *E. S. Rachaman* and *R. W. Jeanloz*, Carbohyd. Res. *10*, 429 (1969).

[88] *I. J. Goldstein* and *W. J. Whelan*, J. Chem. Soc. *1963*, 4264.

[89] *A. Klemer* and *U. Kraska*, Tetrahedron Lett. *1972*, 431.

[90] *D. Shapiro, A. J. Acher, Y. Rabinsohn*, and *A. Diver-Haber*, J. Org. Chem. *36*, 832 (1971).

[91] *T. Suami, S. Ogawa, T. Yoshizawa*, and *S. Umezawa*, Bull. Chem. Soc. Jap. *37*, 1538 (1964); Chem. Abstr. *62*, 1728 (1965).

[91a] *H. Weidmann, D. Tartler, P. Stoeckl*, and *H. Hoenig*, Monatsh. Chem. *103*, 883 (1972).

[92] *K. Heyns, K. Propp, R. Harrison*, and *H. Paulsen*, Chem. Ber. *100*, 2655 (1967).

[93] *B. Helferich* and *W. Ost*, Chem. Ber. *95*, 2612 (1962).

[94] *B. H. Koeppen*, Carbohyd. Res. *13*, 417 (1970).

[95] *B. Helferich* and *O. Arndt*, Liebigs Ann. Chem. *686*, 206 (1965).

[96] *D. M. von Niekerk* and *B. H. Koeppen*, Experientia *28*, 123 (1972).

[97] *C. P. J. Glaudemans* and *H. G. Fletcher*, J. Amer. Chem. Soc. *87*, 2456 (1965); *T. Ueno, N. Kurihara, S. Hashimoto*, and *M. Nakajima*, Agr. Biol. Chem. (Tokyo) *31*, 1346 (1967); Chem. Abstr. *68*, 49923 (1968); *G. J. F. Chittenden*, Carbohyd. Res. *9*, 323 (1969); *Y. Nishimura, T. Tsuchiya*, and *S. Umezawa*, Bull. Chem. Soc. Jap. *44*, 2521 (1971); Chem. Abstr. *75*, 141089 (1971); *K. Takiura, K. Kakehi*, and *S. Honda*, Chem. Pharm. Bull. (Tokyo) *21*, 523 (1973); *T. Suami, T. Otake, T. Nishimura*, and *T. Ikeda*, Carbohyd. Res. *26*, 234 (1973).

[98] *P. F. Lloyd, B. Evans*, and *R. J. Fielder*, Carbohyd. Res. *22*, 111 (1972).

[99] *F. E. Hardy*, J. Chem. Soc. *1965*, 375.

[100] *D. Shapiro*, Chem. Phys. Lipids *5*, 80 (1970); Chem. Abstr. *76*, 34528 (1972).

[101] *W. Meyer zu Reckendorf* and *N. Wassiliadou-Micheli*, Chem. Ber. *103*, 1792 (1970).

[102] *M. L. Wolfrom* and *D. R. Lineback*, Methods Carbohyd. Chem. *2*, 341 (1963).

[103] *M. L. Wolfrom, A. Thompson*, and *D. R. Lineback*, J. Org. Chem. *28*, 860 (1963).

[104] *H. J. Jennings*, Can. J. Chem. *46*, 2799 (1968).

[105] *P. A. J. Gorin*, Can. J. Chem. *40*, 275 (1962).

[106] *W. J. Hickinbottom, J. Chem. Soc. 1929*, 1676.

[107] *A. Ya. Khorlin, A. F. Bochkov, L. V. Bakinovskii*, and *N. K. Kochetkov*, Dokl. Akad. Nauk SSSR *143*, 1119 (1962); Chem. Abstr. *57*, 7354 (1962).

[108] *B. Helferich* and *W. M. Müller*, Chem. Ber. *104*, 671 (1971).

[109] *B. Helferich* and *W. M. Müller*, Chem. Ber. *106*, 941 (1973).

[110] *B. Helferich, W. M. Müller*, and *S. Karbach*, Chem. Ber., in press.

[110a] *R. U. Lemieux* and *H. Driguez*, J. Amer. Chem. Soc., in press.

[110b] *R. U. Lemieux* and *H. Driguez*, J. Amer. Chem. Soc., in press.

[111] *A. Hasegawa, N. Kurihara, D. Nishimura*, and *M. Nakajima*, Agr. Biol. Chem. (Tokyo) *32*, 1123 (1968); Chem. Abstr. *70*, 58215 (1969).

[112] *M. Dejter-Juszynski* and *H. M. Flowers*, Carbohyd. Res. *23*, 41 (1972).

[113] *W. W. Zorbach* and *G. Pietsch*, Liebigs Ann. Chem. *655*, 26 (1962), utilized this reaction in the synthesis of cardiac glycosides with knowledge of the underlying principle.

[114] *H. M. Flowers*, Carbohyd. Res. *18*, 211 (1971).

[115] *S. Koto, T. Uchida*, and *S. Zen*, Chem. Lett. *1972*, 1049; Chem. Abstr. *78*, 30112 (1973).

[116] Review: *R. U. Lemieux* and *T. L. Nagabhushan*, Methods Carbohyd. Chem. *6*, 487 (1972).

[117] *R. U. Lemieux, J. L. Nagabhushan*, and *I. K. O'Neill*, Can. J. Chem. *46*, 413 (1968).

[118] *R. U. Lemieux, T. L. Nagabhushan*, and *K. James*, Can. J. Chem. *51*, 1 (1973).

[119] *K. Miyai* and *R. W. Jeanloz*, Carbohyd. Res. *21*, 45 (1972).

[120] *R. U. Lemieux, R. A. Earl, K. James*, and *T. L. Nagabhushan*, Can. J. Chem. *51*, 19 (1973).

[121] *R. U. Lemieux, K. James*, and *T. L. Nagabhushan*, Can. J. Chem. *51*, 48 (1973).

[122] *N. K. Kochetkov* and *A. F. Bochkov*, Methods Carbohyd. Chem. *6*, 480 (1972).

[123] *N. K. Kochetkov, E. M. Klimov,* and *V. A. Derevetskaya,* Dokl. Akad. Nauk SSSR *192*, 336 (1970); Chem. Abstr. *73*, 88127 (1970); see also Tetrahedron Lett. *1969*, 4769.

[124] *M. Schulz, H.-F. Boeden,* and *P. Berlin,* Liebigs Ann. Chem. *703*, 190 (1967).

[125] *E. Pacsu,* Advan. Carbohyd. Chem. *1*, 77 (1945).

[126] *S. W. Zurabyan, M. M. Tkhomirov, V. A. Nesmeyanov,* and *A. Ya. Khorlin,* Carbohyd. Res. *26*, 117 (1973).

[127] *G. B. Elyakov, N. J. Uvarova,* and *G. J. Oshitok,* Khim.-Farm. Zh. *5*, 7 (1971); Chem. Abstr. *76*, 14850 (1972).

[128] *N. I. Uvarova, G. I. Oshitok,* and *G. B. Elyakov,* Carbohyd. Res. *27*, 79 (1973).

[129] *G. B. Elyakov, N. I. Uvarova, I. V. Dardymov, O. E. Mislitskaya,* and *L. M. Antonik,* Khim.-Farm. Zh. *3*, 5 (1969); Chem. Abstr. *71*, 102179 (1969).

[130] *R. U. Lemieux,* Chem. Can. *16*, 14 (1964).

[131] *G. Alfredsson, H. B. Borén,* and *P. J. Garegg,* Acta Chem. Scand. *26*, 2531 (1972).

[132] *A. I. Bashkatova, V. N. Volynskaya, G. V. Smirnova, V. I. Shvets,* and *R. P. Evstigneeva,* Zh. Org. Khim. *7*, 1542 (1971); Chem. Abstr. *75*, 118525 (1971); *V. I. Shvets, A. I. Bashkatova,* and *R. P. Evstigneeva,* Chem. Phys. Lipids *10*, 267 (1973); Chem. Abstr. *79*, 19031 (1973).

[133] *N. K. Kochetkov, A. F. Bochkov,* and *I. G. Jazlovetsky,* Carbohyd. Res. *9*, 49, 61 (1969).

[134] *A. F. Bochkov, I. V. Obruchnikov,* and *N. K. Kochetkov,* Zh. Obshch. Khim. *42*, 2766 (1972); Chem. Abstr. *78*, 111635 (1973).

[135] *F. Micheel* and *H. Köchling,* Chem. Ber. *91*, 673 (1958), and earlier work.

[136] *S. E. Zurabyan, T. S. Antonenko,* and *A. Ya. Khorlin,* Carbohyd. Res. *15*, 21 (1970).

[137] *K. L. Matta, E. A. Johnson,* and *J. J. Barlow,* Carbohyd. Res. *26*, 215 (1973).

[138] *B. Lindberg,* Acta Chem. Scand. *3*, 1355 (1949).

[139] *H. Lettré* and *A. Hagedorn,* Hoppe-Seylers Z. Physiol. Chem. *242*, 210 (1936).

[140] *E. A. Talley,* Methods Carbohyd. Chem. *2*, 337 (1963).

[141] *K. Freudenberg, A. Noë,* and *E. Knopf,* Ber. Deut. Chem. Ges. *60*, 238 (1927).

[142] *P. Bächli* and *E. G. V. Percival,* J. Chem. Soc. *1952*, 1243.

[143] *I. Karasawa* and *R. Onishi,* Doshisha Joshi Daigaku Gakujutsu Kenkyu Nempo *23*, 433 (1972); Chem. Abstr. *78*, 160055 (1973).

[144] *B. Helferich* and *W. M. Müller,* Chem. Ber. *106*, 715 (1973).

[145] *B. Helferich* and *W. M. Müller,* Chem. Ber. *106*, 2508 (1973).

[146] *S. Haq* and *W. J. Whelan,* J. Chem. Soc. *1958*, 1342.

[147] *R. B. Merrifield,* Advan. Enzymol. *32*, 221 (1969).

[148] *J. M. Fréchet* and *C. Schuerch,* J. Amer. Chem. Soc. *93*, 492 (1971).

[149] *U. Zehavi* and *A. Patchornik,* J. Org. Chem. *37*, 2285 (1972).

[150] *U. Zehavi* and *A. Patchornik,* J. Amer. Chem. Soc. *95*, 5673 (1973).

[151] *G. Excoffier, D. Gagnaire, J. P. Utille,* and *M. Vignon,* Tetrahedron Lett. *1972*, 5065.

[152] *R. D. Guthrie, A. D. Jenkins,* and *G. A. F. Roberts,* J. Chem. Soc. Perkin I *1973*, 2414.

[153] *N. Belorizky, G. Excoffier, D. Gagnaire, J. P. Utille, M. Vignon,* and *P. Vottero,* Bull. Soc. Chim. Fr. *1972*, 4749.

[154] *D. Gagnaire* and *P. Vottero,* Carbohyd. Res. *28*, 165 (1973).

[155] *J. M. Fréchet* and *C. Schuerch,* Carbohyd. Res. *22*, 399 (1972).

[156] *P. J. Pfäffli, S. H. Hixson,* and *L. Anderson,* Carbohyd. Res. *23*, 195 (1972).

[157] *R. D. Guthrie, A. D. Jenkins,* and *J. Stehlíček,* J. Chem. Soc. *C 1971*, 2690.

Phase-Transfer Catalyzed Two-Phase Reactions in Preparative Organic Chemistry

By Eckehard V. Dehmlow[*]

Quaternary ammonium and phosphonium salts catalyze reactions between substances located partly in an aqueous and partly in an organic phase. Use of such phase-transfer catalysts simplifies and accelerates numerous reactions traditionally conducted in nonaqueous media. These reactions include carbene reactions, nucleophilic substitutions, alkylations of ketones and nitriles, Wittig and Darzens reactions, formation of ethers and esters. Other reactions such as hydrolysis and oxidation can be accelerated.

1. Introduction

1.1. Principles and Terminology

Reactions between substances located partly in an organic phase and partly in an aqueous phase are frequently slow and ineffective. Attempts are therefore generally made to obtain all the components, for example in nucleophilic substitutions, in a homogeneous medium. If a hydroxylic solvent is selected many reactions still proceed relatively slowly owing to extensive solvation of the anions; solvolytic side reactions may also interfere. While polar aprotic solvents are often more suitable for such reactions, they are usually more expensive and more difficult to recover; traces of water may sometimes also interfere. Moreover, increased formation of undesirable *O*-alkyl products usually occurs in alkylations of mesoionic anions.

The past few years have witnessed the ascendance of a new technique in which reactions are conducted in aqueous-organic two-phase systems in the presence of an ammonium or phosphonium salt. Typical examples are:

1) Generation of dichlorocarbene from chloroform, concentrated sodium hydroxide, and a few mol-% of triethyl(benzyl)-ammonium chloride.

2) Alkylation of benzyl cyanide in the presence of aqueous sodium hydroxide and a small amount of the above ammonium salt.

3) Reaction of 1-chlorooctane with aqueous sodium cyanide. This can be accomplished in 1.8 hours in 99% yield if 1.3 mol-% of tributyl(hexadecyl)phosphonium bromide is present. Without the catalyst no 1-cyanooctane is formed, even after two weeks' boiling.

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Other variants of such reactions are carried out with molar quantities of the ammonium or phosphonium salt.

The new method has no need of the anhydrous solvents otherwise required and will therefore attract increasing industrial interest. As will be demonstrated in this report, most experience has so far been gained in the fields of carbene generation and alkylation. Nevertheless other reactions (hydrolyses, condensations, oxidations, *etc.*) have also been executed in two-phase systems with catalysts.

No uniform terminology has yet been adopted for the new method. *Brändström*[1] has proposed the term "extractive alkylation" for the specific case of alkylation in the presence of molar amounts of catalyst, and otherwise speaks of applications of ion-pair extraction in preparative organic chemistry. *Makosza* employs expressions such as "catalytic alkylation"[2, 3] and "catalytic development of dihalocarbenes"[4]. The most illustrative term seems to be that of "phase-transfer catalysis"[5, 6] introduced by *C. M. Starks* which will therefore be adopted here.

1.2. Ion-Pair Extraction

This topic leads up to phase-transfer catalysis proper, from both a preparative and a mechanistic viewpoint, and will therefore be considered first.

In analytical and inorganic chemistry, typical ionic compounds are frequently extracted from aqueous solution into organic solvents in the form of ion pairs (for reviews, see refs.[7, 8]). The idea that salts might have a significant solubility in organic phases is relatively strange to the preparative organic chemist. However, *Brändström* and *Gustavii*[9] showed that with suitable solvents it is possible to extract the salts of most amines in almost quantitative yield. Tertiary amines are more readily extracted than their secondary or primary counterparts. A high molecular weight and absence of hydrophilic groups favor extraction. The salts of hydrohalic acids, nitric acid, perchloric acid, tetrafluoroboric acid, and also hydrogen sulfates, azides, cyanides, and nitrites can be transferred to the organic phase without difficulty. Of crucial importance are the following factors:

1) Working concentrations should be as high as possible. Since the ion pairs associate in organic media, unfavorable extraction constants (in dilute solution) can thus be overcome.

2) Choice of solvent is important. *Brändström* and *Gustavii*[9] used an amine bearing hydrophilic side groups as model compound, *viz.* 1-(2-allylphenoxy)-3-isopropylamino-2-propanol, and after a single run under defined conditions were able to extract the following quantities: with chloroform 100%, with 1,2-dichloroethane 93%, with methylene chloride 88%, with ether or carbon tetrachloride 0.6%, with ethyl acetate 16%. Chloroform and methylene chloride will therefore be the extractants of choice.

3) The presence of an excess of anion (as acid or inorganic salt) strongly enhances the extractability of the organic salt.

Given a rough knowledge of their extraction behavior the application of these principles even permits the separation of amines having different structures and properties (*e.g.* primary/secondary; strongly lipophilic/strongly hydrophilic) by simple extraction into chloroform (for details and procedures see ref.[10]).

In the same way as alkylammonium salts of inorganic acids, the salts of weak organic acids can also be extracted and obtained in crystalline form. *Brändström*[11, 12] uses commercially available tetrabutylammonium hydrogen sulfate as standard starting material. It is converted into the ammonium hydroxide by aqueous caustic soda and immediately extracted into a chloroform or methylene chloride solution of the organic compound. Concentration of the organic phase furnishes the pure ammonium salt which is soluble in most organic solvents and can subsequently undergo reaction in anhydrous solvent. The following types of compounds could be extracted as tetrabutylammonium salts[11, 12]: carboxylic acids, phenols, β-diketones, β-cyanoacetic esters, β-keto esters and sulfones, acylmalonic esters, and benzamide. On the other hand, quantitative ion-pair extraction is unsuccessful with still weaker acids such as alcohols, benzyl cyanide, benzyl ketones, aliphatic carbonyl compounds, and malonic esters. However, these compounds can be alkylated by the phase-transfer technique (see Section 2.3).

The isolated tetrabutylammonium salts possess preparative interest on two counts: firstly, they can be alkylated within seconds or minutes; secondly, choice of a suitable solvent can promote *C*-alkylation as against *O*-alkylation compared to the conventional procedure[13–17] (cf. Tables 1 and 2).

Table 1. Isopropylation of tetrabutylammonium pentanedionate [13].

Solvent	*C*-/*O*-Alkylation
DMSO	0.72:1
Acetone	0.72:1
Acetonitrile	0.92:1
Chloroform	1.04:1
Dioxane	1.91:1
Toluene	13.8:1

Table 2. Alkylation of tetrabutylammonium pentanedionate in chloroform [14].

Alkylating agent	Rel. yield [%] mono- + bis-*C*-alkyl	*O*-alkyl	Reaction time [min]
CH_3I	98.5	1.5	10
C_2H_5I	88	12	15
$(CH_3)_2CHI$	50.5	49.5	30
n-C_4H_9I	87	13	15

The pronounced reactivity of the ion pairs in alkylation is explained by the fact that they are only slightly solvated in chloroform and methylene chloride.

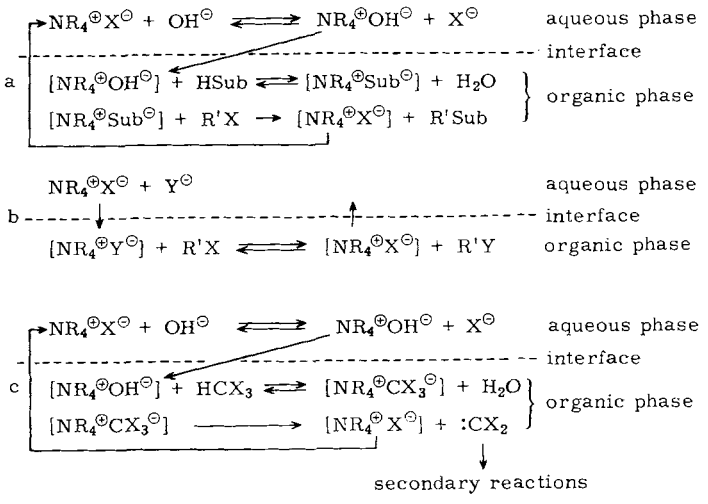
1.3. Course of Phase-Transfer Catalysis

The alkylations discussed above can now be transformed conceptually step by step into phase-transfer catalyzed reactions:

1) Reaction is carried out without isolation of the ammonium salt. Tetrabutylammonium hydrogen sulfate is dissolved in two molar equivalents of sodium hydroxide solution and added dropwise to a molar equivalent of alkyl halide and of the compound to be alkylated. The reaction is often exothermic; the mixture becomes neutral within a few minutes.—This constitutes "extractive alkylation" according to *Brändström*[16]

2) In the next step the procedure is extended to compounds whose low acidity precludes their quantitative extraction as ion pairs (*e.g.* benzyl cyanide, see Section 1.2). The organic phase will then contain both ion pairs and unchanged substrate. Although the local concentration of ion pairs is low, the reactivity of the anion is so high that it is always rapidly removed from the partition equilibrium. Consequently, alkylation takes *ca.* 30 minutes and is sometimes exothermic and sometimes requires heating[1].

3) Reduction of the amount of ammonium ion present to a few mol-% will not cause any fundamental change. A certain concentration of the ion pair will still be present in the organic phase and rapidly be consumed. The ammonium salt migrates back and forth between the phases. It transfers the hydroxide ions as an ammonium hydroxide ion pair from the aqueous phase to the organic medium, where it is converted into an ion pair with the substrate as anion. This is then alkylated. The ammonium salt returns again to the aqueous medium where the hydroxide is regenerated (Scheme 1a).



Scheme 1. Course of phase-transfer catalysis. For details see text. Ion pairs are enclosed in square brackets.

The simpler Scheme 1b applies to other nucleophilic displacements, such as the reaction between cyanide and chlorooctane mentioned in the introduction.

Generation of dihalocarbenes from aqueous sodium hydroxide, ammonium salt, and haloform can likewise be interpreted as in Scheme 1c.

All these reactions can, of course, only proceed quantitatively if the aqueous/organic partition equilibrium permits preferential transfer of $X^{\ominus}$ into the aqueous phase. This is not necessarily always the case. For instance, reaction between cyanide and iodooctane comes to a halt after 5—30% conversion. Replacement of the aqueous phase by fresh cyanide starts the reaction off again until the concentration of iodide once more reaches the equilibrium value. Before attempting an unknown reaction it may be necessary to first examine the partitioning behavior of the anions involved.

That the course of phase-transfer catalysis described above appears reasonable does not constitute proof of its validity. Several authors have considered other possibilities. The catalysts employed are all more or less typical detergents, and hence it was suspected that reaction occurs at the interface[4, 18, 100a] or in a micellar phase[19–23]. Much interest is in fact currently being focused upon the micellar catalysis of a wide range of organic reactions[24]

More detailed mechanistic studies afforded the following evidence which is all in favor of the concepts described: small ions (*e.g.* tetramethylammonium) are not suitable as catalysts. In contrast, large ions (*e.g.* tetrabutylammonium and tetradodecylammonium which are not surfactants) are very effective, regardless of their molecular shape[6, 25, 100b]. In anhydrous nonpolar solvents the salts used undergo only slight association[6]. The mixing speed has no influence on the reaction kinetics once a limiting value for thorough mixing has been reached[6, 28, 100b]. The rate constant of the alkyl halide/-cyanide reaction is proportional to the amount of catalyst and of first order in alkyl halide[5, 6]. The same applies to the reaction of thiophene oxide with 1-bromooctane in benzene/water in the presence of various catalysts[100b]. On solvolysis of 2-bromooctane with aqueous sodium hydroxide/ammonium salt catalyst, an elimination-substitution ratio was found that is typical of reaction in anhydrous media[25, 26]. Finally, the anion transfer equilibrium aqueous phase/organic phase can be determined. It depends upon the relative concentrations, the amount of water present, and the polarity of the organic medium[6].

Selectivity data for dichlorocarbene generation are available[5] which show that the same kind of free dichlorocarbene species is formed as in other methods[27]. However, the actual phase-transfer process has not yet been subjected to kinetic analysis. Nevertheless, the only question open to conjecture is whether the reaction with solvent chloroform already occurs at the interface[100a] or, at least in part, after penetration into the organic phase. Formerly dihalocarbenes were generally assumed to be exceptionally sensitive to moisture, since chloroform is known to undergo hydrolysis to formate. It was found, however, that the carbene formed by the phase-transfer technique undergoes further reaction so rapidly that it is hardly hydrolyzed. This would contraindicate formation of the major portion of the carbene at the interface.

2. Preparative Applications

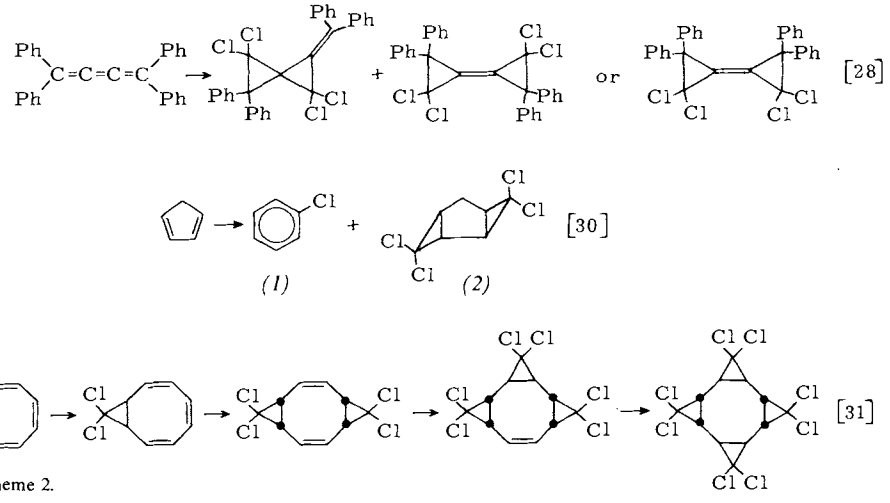
2.1. α-Elimination

2.1.1. Dichlorocarbene Additions (Mąkosza Reaction)

The preferred catalyst for generation of dihalocarbenes from haloform with 50% sodium hydroxide is triethyl(benzyl)ammonium chloride[4]. However, trihexyl(methyl)-[5] and cetyltrimethylammonium chloride[19] are also recommended. The inexpensive reagents chloroform and caustic soda are best employed in large excess[28].

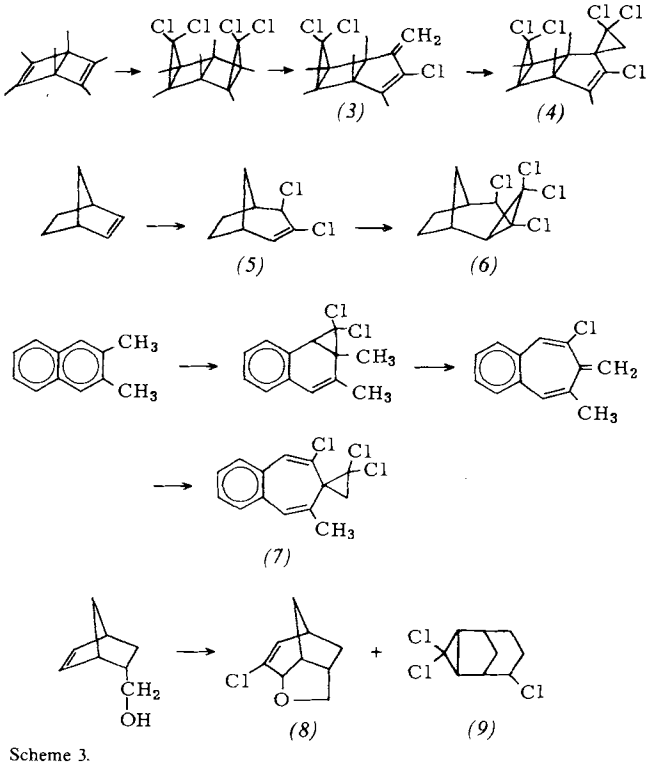
Selectivity comparisons of addition of CCl_2 to normal olefins were mentioned in Section 1.3. If relatively unreactive substances are presented to the carbene a complicated situation will arise: the highly reactive CCl_2 can react with the substrate, the solvent, itself, or its precursor. Dihalocarbene will therefore display various "net reactivities" towards "poor" substrates. It is found that the CCl_2 generated by phase-transfer reaction is exceptionally reactive towards substrates which hardly react, if at all, with conventionally generated dichlorocarbene (*e.g.* from potassium *tert*-butoxide and chloroform). This is because the carbene is formed close to its site of further reaction and a large excess is easily generated.

Apart from normal alkenes and enol ethers[4, 5, 19], the Makosza reaction can also be used to dichlorocyclopropanate sterically hindered olefins (*e.g.* triphenylethylene) and electron-deficient olefins (*e.g.* methacrylonitrile), as well as acetylenes[*][28, 29]. However, addition is no longer observed with tetraphenylethylene and the di-, tri-, and tetrachloroethylenes.—Conventional dihalocarbene reagents usually add only once to conjugated olefins; electron withdrawal by the chlorine atoms deactivates the molecule towards a second attack. Single and multiple additions can easily be accomplished with "phase-transfer dichlorocarbene" depending upon the reaction conditions[28, 30, 31]. Schemes 2 and 3 show typical examples.



Scheme 2.

The isolation of tricycloheptane *(2)* deserves particular attention. The corresponding monoadduct is transformed into *(1)* extremely readily by base. In other cases multiple adducts are



Scheme 3.

[*] Hydrolysis to secondary products occurs here: cyclopropenones and conjugated acetylenic ketones are formed [28, 57].

final products of a series of reactions [*(4)*, *(6)*, *(7)*]. The intermediate *(3)* can be obtained with dichlorocarbene from potassium *tert*-butoxide/chloroform[30a]. Depending on the conditions the major product from norbornene can be chosen as *(5)* or *(6)*[32]. *Weyerstahl et al.* observed conversion of alkylaromatic compounds into spirononatrienes by CCl_2. Formation of *(7)* is typical; alkylbenzenes usually afford several isomers[33]. In other cases side groups participate in the reaction, *e.g.* with *(8)* and *(9)*[34]. Ring enlargements occur with 1,4,5,8-tetramethoxynaphthalene and tetramethylpurpurogallin to yield substituted benzocyclooctatrienones and 2,3-benzohomotropones[101].

Further experience is available concerning the reactions of dichlorocarbene generated by phase-transfer catalysis with the following types of substrates: sterically hindered arylated olefins[28, 35, 36], ferrocene-substituted alkenes[37], steroidal olefins[38], methylfurans and -thiophenes[33b], phenanthrene[39], indenes[52], bicyclo[2.2.1]heptenes[32, 40] and -heptadienes[30], enolacetates of bicyclo[3.2.1]octanones[41], Schiff bases[53], and enamines[54] (for general procedure see footnote[*]).

2.1.2. Insertions of Dichlorocarbene

C—H insertion reactions of dichlorocarbene generated conventionally from potassium *tert*-butoxide and chloroform or with sodium methoxide/trichloroacetic ester are rare and give poor yields. Somewhat better results are obtained on generation from sodium trichloroacetate[42], and even better ones on preparation from bromodichloromethyl(phenyl)mercury[43].

Dichlorocarbene generated by phase-transfer catalysis also displays an enhanced net reactivity since it is formed in the immediate vicinity of the substrate and is less likely to undergo undesirable side reactions with the solvent or with itself. Nevertheless, yields of preparative utility only occur on inser-

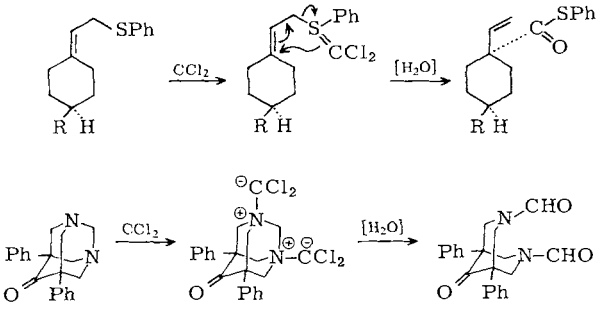
[*] Substrate (0.5 mol) and triethyl(benzyl)ammonium chloride (1 g) are dissolved in chloroform (500 g) and vigorously stirred with 50% NaOH (500 g), first at 0 °C and then at room temperature. After *ca.* 12 h the reaction mixture is poured into a large volume of water, separated, and reextracted with chloroform. Brownish, insoluble deposits (polymeric CCl_2?) are disregarded. Any stubborn emulsions which may occur are destroyed by repeated slow pouring into fresh water. After drying the organic phase is drawn off and purified by distillation, crystallization, or chromatography [28].—Other variants employ molar amounts of substrate/chloroform/caustic soda at 45 °C (dropwise addition of the chloroform) with stirring of the reaction mixture for only 1 h [4, 5].

tion into bridgehead positions or α to activating groups. A striking difference is observed with the isomeric decalins: only the *cis* compound with an exposed tertiary hydrogen reacts well. In a number of cases[20, 22] the chloroform is added dropwise at 65 °C to the two-phase system substrate-in-benzene/NaOH. Generally, however, the same procedure (see Section 2.1.1) is adopted as for addition (cf. Table 3).

Table 3. C—H insertions of dichlorocarbene.

Compound	Position of insertion	Yield [%]	Ref.
Cumene	1-	22, 18	[44, 45]
Ethylbenzene	1-	2	[45]
Tetralin	1-	21	[45]
Methylcyclohexane	1-	4	[44]
Trishomobarrelene	1-	60	[46]
cis-Decalin	9-	29	[44]
trans-Decalin	9-	< 3	[44]
Adamantane	1-	54	[20]
Diamantane	1-	63	[22]
	4-	37	
Methoxycyclohexane	1-	5	[44]
THF	2-	18	[45]
Diisopropyl ether	1-	13	[44]
1-Methyl-1,2-dihydroquinoline	2- and 4-	30	[47]

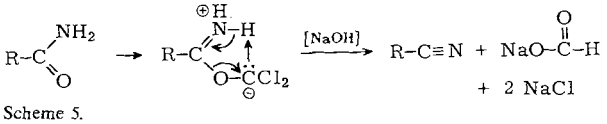
Formal insertions into C—S bonds[48] and C—N bond rupture[49] have also been observed (Scheme 4). They appear to begin with attack at the heteroatom.



Scheme 4.

2.1.3. Nitriles from Amides with Dichlorocarbene

Independently of each other, *Saraie et al.*[50] and *Höfle*[51] found that aromatic and aliphatic amides, thioamides, aldoximes, and ureas are converted into nitriles by dichlorocarbene from a phase-transfer reaction (for general procedure see footnote[*]). The yield lies between 10 and 20% for lower aliphatic amides and up to 95% for lipophilic (long-chain or branched) compounds. Hydrolysis predominated with the lower compounds and some bisamides. The reaction mechanism of Scheme 5 appears plausible.



Scheme 5.

[*] A carboxamide (50 mmol) and triethyl(benzyl)ammonium chloride (2.2 mmol) are dissolved or suspended in chloroform (30 ml), warm 40% NaOH (50 ml, 0.7 mol) is added and the reaction mixture refluxed for 30 min. Reaction is stopped by cooling and addition of chloroform (*ca.* 50 ml) and the mixture is separated. After washing with 2 N HCl (2 ml) and drying over $MgSO_4$, the solvent is drawn off and the nitrile purified by distillation or sublimation [51].

2.1.4. Preparation of Isocyanide

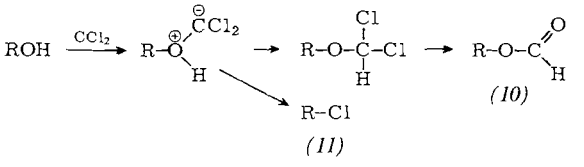
The well-known carbylamination reaction

$$R{-}NH_2 \rightarrow R{-}N{\equiv}C:$$

usually gives modest and poorly reproducible yields, shortcomings which can be rectified in the phase-transfer version of the reaction[55, 56]. Yields of between 20 and 60% are obtained on use of molar amounts of amine and chloroform or bromoform. Presumably much higher yields can be obtained, as in the addition and insertion reactions, if the inexpensive reagents are used in excess.

2.1.5. Conversion of Alcohols into Chlorides by Dichlorocarbene

Tabushi et al.[21] discovered that phase-transfer generation of dichlorocarbenes in the presence of alcohols usually gives only small amounts of the expected formates *(10)*; alkyl chlorides *(11)* are formed instead. This reaction appears to be very general[21, 29, 57] and gives high yields. Rearrangements sometimes occur, thus suggesting carbonium ion intermediates.



(10)

(11)

2.1.6. Bisdehydroxylation of Glycols

Preliminary experiments with α-glycols showed varying modes of product formation with dichlorocarbene under phase-transfer conditions: *cis*-1,2-cyclooctanediol yields a mixture of cyclooctanone and cyclooctene and its dichlorocarbene adduct, whereas *meso*-dihydrobenzoin was transformed into *cis*-stilbene and *trans*-stilbene oxide[102].

2.1.7. Other Halocarbenes

In principle, the generation and reaction of dibromocarbene can be performed in exactly the same way as for dichlorocarbene[28, 58-61]. However, yields are somewhat lower if the procedure is adopted without modification. The depleted reactivity of bromoform compared to chloroform is also apparent from the exclusive formation of CCl_2 in a competition experiment[59]. *Skattebol* demonstrated that a two- to four-fold molar excess of bromoform and a prolonged reaction time (48—92 h) can give very good yields[60] in many cases. *Makosza et al.* propose working with a twofold molar excess of bromoform in presence of a small amount of ethanol (0.8 ml with 0.4 mol of $HCBr_3$)[61]. They assume a specific solvation and stabilization of the tribromomethylide-triethyl(benzyl)ammonium ion pair by ethanol.

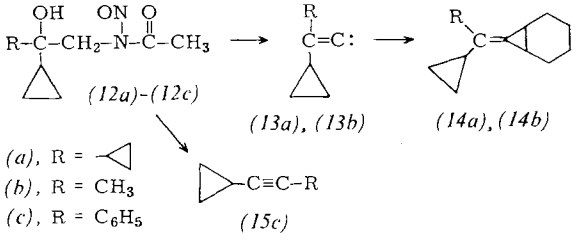
1,1-Diiodocyclopropanes were hitherto assumed to be not isolable. They have recently become available from iodoform by phase-transfer catalytic generation of diiodocarbene in methylene chloride/aqueous sodium hydroxide/olefin mixtures[103]. Some of these compounds are stable at −30 °C over long periods of time. Similarly, olefin adducts of chloroiodocarbene can be obtained from chlorodiiodomethane[103]. Bromofluorocarbene[62], chlorofluorocarbene[62, 63], and

fluoroiodocarbene[64] can likewise be generated from dibromofluoromethane, dichlorofluoromethane, and fluoroiodomethane, respectively, with caustic soda and triethyl(benzyl)ammonium chloride. Stirring of the reaction mixture for 1—4 h appears to suffice for yield maximization. Addition of ClCF to a substrate having a free hydroxy group proceeds without complications (cf. Section 2.1.5)[63]. The facile production of iodine-containing carbenes from polyiodomethanes is remarkable since phase-transfer reactions are frequently inhibited by iodide ion. The iodide ion transfers preferentially to the organic phase[2,5]. Methylene chloride serves as cosolvent in all these preparations.

The basicity of the two-phase system is insufficient to convert methylene chloride and bromide into the carbenes, even if the reaction is conducted at elevated temperatures in an autoclave[57]. Attempts to generate chlorophenylcarbene from benzylidene chloride were likewise unsuccessful. However, it proves possible to scavenge adducts of chloro(phenyl)thiocarbene (2 hours' reaction at 40—50 °C)[18]. Small quantities of 1,2-dichloro-1,2-bis(phenylthio)ethylene occur as by-product. Chloro(methyl)thiocarbene behaves similarly[82].

2.1.8. Alkylidenecarbenes

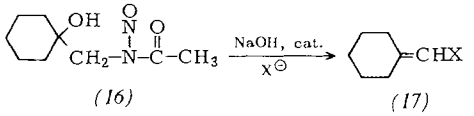
Treatment of *N*-hydroxyalkyl-*N*-nitrosoacetamides having structure *(12a)* and *(12b)* in pentane/cyclohexene with caustic soda in the presence of catalytic amounts of trihexyl(methyl)ammonium chloride leads to the alkylidenecarbenes *(13a)* and *(13b)* respectively. These carbenes are scavenged, *e.g.* by cyclohexene, as *(14a)* and *(14b)*. With *(12c)*, however, rearrangement to acetylenes *(15c)* occurs instead[65]. Cyclohexylidenecarbene can be generated and scavenged similarly[66]. If *(16)* is decomposed in the presence of nucleophiles (X = azide, iodide, thiocyanate, *etc.*), the compounds *(17)* can be isolated. With isobutyraldehyde and cyclohexanone, *(16)* furnishes the compounds *(18)* and *(19)* respectively. Intermediacy of the carbene has yet to be established[67].



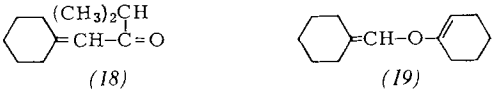
(12a)-(12c) *(13a), (13b)* *(14a), (14b)*

(a), R =
(b), R = CH_3
(c), R = C_6H_5

(15c)



(16) *(17)*

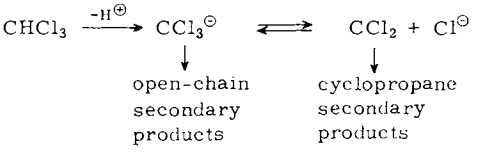


(18) *(19)*

2.2. Reactions of Trihalomethyl Anions

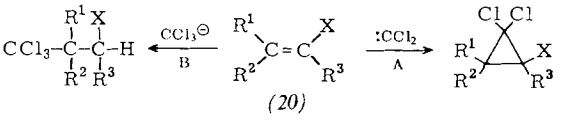
2.2.1. Addition of Chloroform to Double Bonds

As shown in Section 1.3, the primary product of the phase-transfer reaction between sodium hydroxide and chloroform is the trichloromethyl anion (in the form of its ion pair). It is in equilibrium with dichlorocarbene and chloride ion (Scheme 6).



Scheme 6.

Depending upon whether electron-rich or electron-poor olefins are present, either the electrophilic CCl_2 or the nucleophilic $CCl_3^{\ominus}$ is scavenged from the equilibrium, or in some cases both[29,68,69]. The direction of the reaction is affected by small changes in electron distribution, as is apparent from Table 4. Analogous reactions occur with bromoform.



(20)

Table 4. Reactions of compounds *(20)* with chloroform, sodium hydroxide, and triethyl(benzyl)ammonium hydroxide as catalyst [29,69].

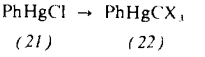
(20)	R^1	R^2	R^3	X	Direction
(a)	H	H	H	OAc	B
(b)	H	H	H	CN	B
(c)	H	H	CH_3	CN	A + B
(d)	CH_3	H	H	CN	B
(e)	Ph	H	H	CN	B
(f)	H	H	H	SO_2R	B
(g)	H	H	H	COOR	B
(h)	H	H	CH_3	COOR	A
(i)	H	CH_3	CH_3	COOR	A
(j)	CH_3	H	H	COOR	A [a] + B
(k)	CH_3	CH_3	H	COOR	A [a]
(l)	H	Ph	H	COOR	A [a]

[a] Followed by a secondary reaction, see Section 2.2.3.

Hydrolysis of the nitrile and ester plays a very minor role. α,β-Unsaturated carbonyl compounds mainly polymerize under the reaction conditions.

2.2.2. Nucleophilic Substitution by $CX_3^{\ominus}$

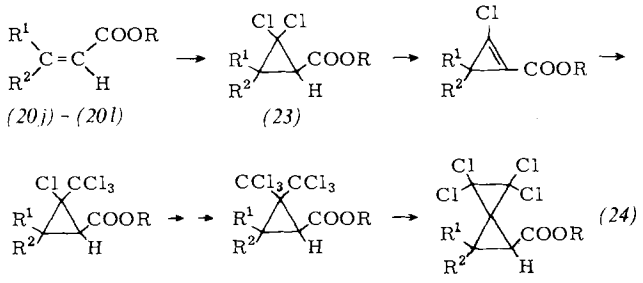
Trihalomethyl(phenyl)mercurials *(22)* are important halocarbene precursors. On moderate heating they generate the carbene without intervention of the $CX_3^{\ominus}$ ion[71]. The hitherto difficult preparation of these compounds is improved by the phase-transfer catalyzed reaction. A solution of 20 g sodium hydroxide and 37 g potassium fluoride per 100 g of water is treated with a suspension of 0.05 mol *(21)* and 0.4 g triethyl(benzyl)ammonium chloride in CHX_3 at 20 °C[70].



(21) *(22)*

2.2.3. Formation of Tetrachlorospiropentanes

Tetrachlorospiropentanes *(24)* are formed on reaction of *(20j)—(20l)* with the caustic soda/haloform/catalyst system[29]. *(23)* occurs as intermediate[57]. Two successive cycles of dehydrochlorination and addition of $CX_3^{\ominus}$ take place. The last step is initiated by $Cl^{\oplus}$ abstraction from the molecule by trichloromethylide. This type of reaction can also be performed with α,β-unsaturated steroidal ketones[57].



(20j) - (20l) (23) (24)

2.3. Alkylation of Carbanions

A great deal of information has accumulated about alkylations with simple and more complicated monohalo and bishalo compounds and about the promotion of *C- vs. O*-alkylation (see Section 1.2[104]).

Table 5 provides a survey of the classes of compounds so far alkylated by the phase-transfer method. The quaternary ammonium salts of relatively strong C—H acids can be isolated and then subjected to further reaction (cf. refs.[13–15, 17]). More weakly acidic compounds can only be alkylated catalytically. Depending upon the structure of the carbanion and alkylating agent, mono-*C*-alkylation predominates on suitable choice of the molar ratios. Simple aldehydes are prone to self-condensation under the reaction conditions. Hence the method can be applied only to the reaction of aldehydes bearing an α-hydrogen with reactive alkyl or benzyl halides if high yields of preparative interest are desired (for procedure see footnote[*]). Detailed investigations of the dependence of yields of such alkylations upon the type of catalyst used were performed in isolated cases[100b, 106].

Table 5. Compounds alkylated by phase-transfer catalysis [a].

Class of cpd.	Ref.
Substituted phenylacetonitriles	[1, 2, 5, 73, 87, 104]
Phenylthioacetonitrile	[74]
Benzyl ketones	[1, 75, 76, 104]
Simple ketones	[76]
Aldehydes	[72]
β-Keto esters	[16]
Malonic ester	[1, 105]
Malononitrile	[5]
Phenylacetic ester	[105]
Indene	[77]
Fluorene	[78]
Indolone	[79]
1-Benzothiophen-2(3*H*)-one	[80]
3-Mercaptocrotonic esters	[81]
β-Keto sulfones	[83]
2-Hydroxythiophenes and -furans	[84]
Hydrazobenzenes	[85]
1,4-Benzodiazepin-3-one	[86]

[a] For a structural tabular survey of individual substrates and alkylating agents including yields, see ref. [106].

[*] *2,2-Dimethyl-3-phenylpropanol:* A mixture of NaOH (140 g, 3.5 mol), water (140 g), benzene (200 ml), and tetrabutylammonium iodide (14.7 g, 0.04 mol) is heated to 70 °C. A mixture of isobutyraldehyde (288 g, 4 mol) and benzyl chloride (380 g, 3 mol) is added dropwise over a period of 5 h with stirring. Stirring is then continued for 2 h. Distillation of the organic phase affords 364 g (75 %) of product having b. p. 95 °C/7.2 torr [72].

Alkylation of malonic ester, benzyl cyanide, or benzyl methyl ketone: A mixture of the substrate (0.1 mol) and alkyl iodide (0.2 mol) in CH_2Cl_2 (100 ml) is added dropwise to a stirred mixture of tetrabutylammonium hydrogen sulfate (0.1 mol) and sodium hydroxide (0.2 mol) in water (100 ml). With methyl iodide the reaction is exothermic and complete within 10 min; with *n*-butyl iodide the mixture is boiled for 30 min. After phase separation the methylene chloride is evaporated off under reduced pressure. Tetrabutylammonium iodide is precipitated by addition of ether to the residue. Filtration is followed by distillation.—Variants of the method employ only 2—5 mol-% of catalyst and triethyl(benzyl)ammonium chloride or other salts [1].

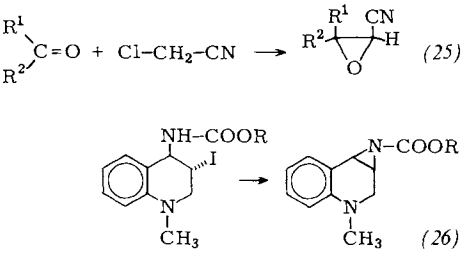
2.4. Alkylation of Other Anions

2.4.1. Esterification

Esterifications can be accomplished in neutral solution by neutralizing one equivalent of acid and one equivalent of tetrabutylammonium hydrogen sulfate with two mol of aqueous sodium hydroxide and boiling the resulting mixture with the alkylating agent for 15—30 min[88, 89]. Almost quantitative yields are obtained even with sterically hindered acids (*e.g.* 2,4,6-trimethylbenzoic acid)[89]. The method can also be applied to dicarboxylic acids but finds its match with very hydrophilic compounds: tartaric acid is esterified in only 40 % yield.—When dimethyl sulfate is used as alkylating agent only 10 mol-% of catalyst are required[89].

2.4.2. Darzens Reaction to Give Oxiranes and Formation of Aziridines

The oxirane *(25)*[90] and the aziridine *(26)*[91] have recently been prepared by phase-transfer catalysis.



(25)

(26)

2.4.3. Ether Formation

The catalytic version of the Williamson ether synthesis[25] gives high yields in the case of symmetrical ethers (from alkyl halide, caustic soda, and catalyst). However, reaction of alcohol and alkyl halide bearing different groups yields a mixture of symmetrical and unsymmetrical ethers.

Very recently it was reported that high yields of methyl ethers can be obtained from saturated primary alcohols as well as from primary, secondary, and tertiary alcohols activated by electron-withdrawing or unsaturated groups with dimethylsulfate/aqueous sodium hydroxide/tetrabutylammonium hydroxide catalyst at 45 °C. Even neopentyl alcohol can be reacted[108].

2.4.4. Nucleophilic Displacements

The reaction

$$RX + Y^{\ominus} \rightarrow RY + X^{\ominus}$$

can be drastically accelerated by phase-transfer catalysis. The systems investigated contained chloride, bromide, iodide, methanesulfonate, and *p*-toluenesulfonate as leaving groups

and cyanide, bromide, acetate, iodide, thiocyanate, and cyanate as nucleophiles[5, 92, 100b]. If $X^{\ominus}$ is iodide or *p*-toluenesulfonate the reaction stops on reaching the phase partioning equilibrium of the anions. Thus the aqueous phase must be renewed several times to ensure complete reaction. In other cases (*e.g.* X = Br, Y = Cl) the progress of the reaction is halted by the chemical equilibrium. Here, too, the aqueous phase must be replaced to achieve complete reaction (for procedure see footnote[*]).

Primary C_4 to C_{16} alcohols have been converted into chlorides by boiling with conc. hydrochloric acid in presence of hexadecyl(tributyl)phosphonium bromide[109]. Average yields were around 60% after 8 h, and rose to 95% after 45 h.

In many cases the hydrolysis of esters and alkanesulfonyl chlorides is likewise accelerated by addition of a quaternary ammonium salt. Reaction is frequently exothermic and requires no external heating. On application of the technique to esters of long-chain acids the acid anions preferentially associate with the ammonium ion and hydrolysis remains incomplete or proceeds as slowly as if no catalyst were present[5].

2.5. Other Reactions Accelerated by Phase-Transfer Catalysis

2.5.1. Oxidation by $KMnO_4$

In the presence of trihexyl(methyl)ammonium chloride, neutral aqueous permanganate oxidizes terminal olefins to the carboxylic acids having one less carbon atom[5]. The reaction is exothermic; the temperature is maintained at 35—45 °C by the rate of olefin addition (cf. also ref.[100b]). Strongly basic aqueous permanganate with triethyl(benzyl)ammonium chloride as catalyst converts nonterminal olefins into *cis*-glycols in CH_2Cl_2 at 0 °C[93].

2.5.2. Replacement of Active Hydrogen Atoms by Deuterium

In the case of ketones replacement can be conducted with $NaOD/D_2O$/catalyst within 30 min at 30 °C[5].

2.5.3. Reductions with Boron Hydrides

Tetraalkylammonium tetrahydridoborate can be extracted quantitatively into CH_2Cl_2 from the caustic soda/tetraalkylammonium salt/$NaBH_4$ system when the alkyl groups contain 12 or more carbon atoms. After drying, this solution is added to the substrate to be reduced with methyl iodide which liberates diborane[94] according to

$$2BH_4^{\ominus} + 2CH_3I \rightarrow B_2H_6 + 2CH_4 + 2I^{\ominus}$$

Quite analogously, one can prepare solid tetrabutylammonium cyanotetrahydridoborate[110]. This reagent is useful for the reduction of iodides and bromides at room temperature in hexamethylphosphoramide solvent. Under these conditions carbonyl groups, amides, cyanides, and aromatic nitro groups are not affected. In the presence of 0.1 N acid, however, aldehydes are reduced while ketones are not attacked at room temperature.

2.5.4. Benzoin Condensation

Tetrabutylammonium cyanide permits the benzoin condensation to be carried out in water at room temperature within 1.25 h[95].

2.5.5. Wittig Reaction

Märkl and *Merz* recently showed that non-stabilized phosphonium salts can also be deprotonated with caustic soda in methylene chloride[96]. Since phosphonium salts are themselves phase-transfer catalysts, no ammonium salt is necessary. In the presence of aldehydes, Wittig reaction is faster than the undesired degradation to phosphane oxide. In the examples described R^1 is aryl or styryl; R^2/R^3 is H, CH_3, or phenyl. Yields between 20 and 88% are reported (for procedure see footnote[*]).

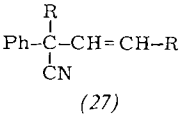
$$R^1CHO + Ph_3\overset{\oplus}{P}-CHR^2R^3 \xrightarrow{CH_2Cl_2,\,NaOH} R^1CH{=}CR^2R^3 + Ph_3PO$$

2.5.6. Other Reactions

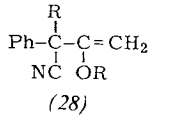
A sulfur ylide can be generated from trimethylsulfonium iodide in the system methylene chloride/aqueous sodium hydroxide/tetrabutylammonium salt. Reaction with benzaldehyde gives *e.g.* 90% 2-phenyloxirane within 48 h at 50 °C[111]. Ketones give rise to lower yields. In a similar fashion, trimethyloxosulfonium iodide is transformed into the related ylide which is useful for the formation of cyclopropyl ketones from aromatic α,β-unsaturated ketones[111].

If conjugated olefins are formed HX eliminations can be accelerated by phase-transfer catalysis[106]. An investigation of the effectiveness of *n*-alkyl(triethyl)ammonium salts relative to the chain lengths showed maximum activity with the *n*-hexyl compound. The catalytic effect decreased strongly towards shorter chains but only slightly towards longer alkyl groups[106].

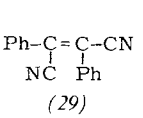
Catalyzed addition of phenylacetonitrile to acetylenes affords *(27)* (R = H, Ph, SR) or, in the case of ethoxyacetylene, *(28)*[97, 98]. DMSO/solid NaOH/catalyst is used here.



(27)



(28)



(29)

The catalytic reaction of phenylacetonitrile with CCl_4 to yield *(29)* also deserves mention[99].

[*] *1-Decyl acetate:* 1-Bromodecane (55 g, 0.25 mol), Na-acetate·$3H_2O$ (270 g, 1.98 mol), and trihexyl(methyl)ammonium chloride (10 g) are stirred for 1 h at 105 °C. Gas chromatography indicates practically quantitative reaction [92].

1-Thiocyanatodecane: A mixture of 1-bromodecane (100 g, 0.45 mol), NaSCN (160 g, 7.98 mol), water (50 ml), and trihexyl(methyl)ammonium chloride is stirred for 2 h at 88—105 °C. Gas chromatography indicates quantitative reaction of the bromodecane [92].

[*] *cis- and trans-Stilbene:* 50% caustic soda (10 ml) is run into a vigorously stirred mixture of benzaldehyde (2.06 g, 20 mmol), benzyl(triphenyl)phosphonium iodide (7.86 g, 20 mmol), and CH_2Cl_2 (10 ml). A weakly exothermic reaction ensues which is complete after *ca.* 10 min. The organic phase is separated off, washed with water, dried, and the solvent removed under reduced pressure. Addition of ethanol (15 ml) and cooling in an ice bath induces crystallization of *trans*-stilbene [m. p. 123—124 °C, yield 1.2 g (33%)]. Vacuum distillation of the filtrate affords *cis*-stilbene [b. p. 60- -62 °C/0.01 torr, $n_D^{20} = 1.6215$, yield 1.7 g (47%)] [96].

3. Outlook

The first publications on phase-transfer catalysis, which appeared in Polish in 1965, attracted little attention. Since about 1969, the method has been adopted by several research groups and publicized. Steadily increasing interest has been the result. Owing to its simplicity and the low cost of the reagents, the method should soon find universal application, not least in many technical processes. We can predict that it will be extended to more and more types of reaction. It is the author's wish to have stimulated the readers' imagination in this respect.

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[1] *A. Brändström* and *U. Junggren*, Tetrahedron Lett. *1972*, 473.

[2] *M. Makosza* and *B. Serafinowa*, Rocz. Chem. *39*, 1223, 1401, 1595, 1799, 1805 (1965); *40*, 1647, 1839 (1966).

[3] *M. Makosza*, a) Tetrahedron Lett. *1969*, 673; b) *ibid. 1969*, 677.

[4] *M. Makosza* and *W. Wawrzyniewicz*, Tetrahedron Lett. *1969*, 4659.

[5] *C. M. Starks*, J. Amer. Chem. Soc. *93*, 195 (1971).

[6] *C. M. Starks*, J. Amer. Chem. Soc. *95*, 3613 (1973).

[7] *G. H. Morrison* and *H. Freiser*: Solvent Extraction in Analytical Chemistry. Wiley, New York 1957.

[8] *Y. Markus*, Chem. Rev. *63*, 139 (1963).

[9] *A. Brändström* and *K. Gustavii*, Acta Chem. Scand. *23*, 1215 (1969).

[10] *K. Gustavii*, *A. Brändström*, and *S. Allansson*, Acta Chem. Scand. *25*, 77 (1971).

[11] *A. Brändström*, *P. Berntsson*, *S. Carlsson*, *A. Djurhuus*, *K. Gustavii*, *U. Junggren*, *B. Lamm*, and *B. Samuelsson*, Acta Chem. Scand. *23*, 2202 (1969).

[12] Review (in Swedish): *A. Brändström*, Kemi. Tidskr. *82*, 32 (1970).

[13] *A. Brändström* and *U. Junggren*, Acta Chem. Scand. *25*, 1469 (1971).

[14] *A. Brändström* and *U. Junggren*, Acta Chem. Scand. *23*, 3585 (1969).

[15] *A. Brändström* and *U. Junggren*, Acta Chem. Scand. *23*, 2203 (1969).

[16] *A. Brändström* and *U. Junggren*, Acta Chem. Scand. *23*, 2204 (1969).

[17] *A. Brändström* and *U. Junggren*, Acta Chem. Scand. *23*, 2536 (1969).

[18] *M. Makosza* and *E. Bialecka*, Tetrahedron Lett. *1971*, 4517.

[19] *G. C. Joshi*, *N. Singh*, and *L. M. Pande*, Tetrahedron Lett. *1972*, 1461.

[20] *I. Tabushi*, *Z. Yoshida*, and *N. Takahashi*, J. Amer. Chem. Soc. *92*, 6670 (1970).

[21] *I. Tabushi*, *Z. Yoshida*, and *N. Takahashi*, J. Amer. Chem. Soc. *93*, 1820 (1971).

[22] *I. Tabushi*, *Y. Aoyama*, and *N. Takahashi*, Tetrahedron Lett. *1973*, 107.

[23] *C. Lapinte* and *P. Viout*, Tetrahedron Lett. *1973*, 1113.

[24] Reviews: *E. H. Cordes* and *R. B. Dunlap*, Accounts Chem. Res. *2*, 329 (1969); *E. J. Fendler* and *J. H. Fendler*, Advan. Phys. Org. Chem. *8*, 271 (1970).

[25] *A. W. Herriott* and *D. Picker*, Tetrahedron Lett. *1972*, 4521.

[26] Interestingly, comparable results in another system [25] are tacitly regarded as of a micellar nature [23].

[27] *P. S. Skell* and *M. S. Cholod*, J. Amer. Chem. Soc. *91*, 6035, 7131 (1969); *G. Köbrich*, *H. Büttner*, and *E. Wagner*, Angew. Chem. *82*, 177 (1970); Angew. Chem. internat. Edit. *9*, 169 (1970).

[28] *E. V. Dehmlow* and *J. Schönefeld*, Liebigs Ann. Chem. *744*, 42 (1971).

[29] *E. V. Dehmlow*, Liebigs Ann. Chem. *758*, 148 (1972).

[30] a) *E. V. Dehmlow*, Tetrahedron *28*, 175 (1972); b) *S. Dehmlow* and *E. V. Dehmlow*, Liebigs Ann. Chem. *1973*, 1753.

[31] *E. V. Dehmlow*, *H. Klabuhn*, and *E.-Ch. Hass*, Liebigs Ann. Chem. *1973*, 1063.

[32] *W. Kraus*, *G. Klein*, *H. Sadlo*, and *W. Rothenwöhrer*, Synthesis *1972*, 485; *C. W. Jefford*, *U. Burger*, and *F. Delay*, Helv. Chim. Acta *56*, 1083 (1973).

[33] *P. Weyerstahl* and *G. Blume*, a) Tetrahedron Lett. *1970*, 3669; b) Tetrahedron *28*, 5281 (1972).

[34] *T. Sasaki*, *S. Eguchi*, and *T. Kiriyama*, J. Org. Chem. *38*, 2230 (1973).

[35] *S. Kajigaeshi*, *N. Kuroda*, *G. Matsumoto*, *E. Wada*, and *A. Nagashima*, Tetrahedron Lett. *1971*, 4887.

[36] *F. Effenberger* and *W. Kurtz*, Chem. Ber. *106*, 511 (1973).

[37] *G. W. Gokel*, *J. P. Shepherd*, and *W. P. Weber*, J. Org. Chem. *38*, 1913 (1973).

[38] *R. Ikan*, *A. Markus*, and *Z. Goldschmidt*, J. C. S. Perkin I *1972*, 2423.

[39] *G. C. Joshi*, *N. Singh*, and *L. M. Pande*, Synthesis *1972*, 317.

[40] *C. M. Jefford*, *A. Sweeney*, and *F. Delay*, Helv. Chim. Acta *55*, 2214 (1972).

[41] *W. Kraus*, *W. Rothenwöhrer*, *H. Sadlo*, and *G. Klein*, Angew. Chem. *84*, 643 (1972); Angew. Chem. internat. Edit. *11*, 641 (1972).

[42] *E. K. Fields*, J. Amer. Chem. Soc. *84*, 1744 (1962).

[43] *D. Seyferth*, *J. M. Burlitch*, *K. Yamamoto*, *S. S. Washburne*, and *C. J. Attridge*, J. Org. Chem. *35*, 1989 (1970).

[44] *E. V. Dehmlow*, Tetrahedron *27*, 4071 (1971).

[45] *M. Makosza* and *M. Fedorynski*, Rocz. Chem. *46*, 311 (1972).

[46] *A. de Meijere*, *O. Schallner*, and *C. Weitemeyer*, Angew. Chem. *84*, 63 (1972); Angew. Chem. internat. Edit. *11*, 56 (1972).

[47] *T. Greibrokk*, Tetrahedron Lett. *1972*, 1663.

[48] *G. Andrews* and *D. A. Evans*, Tetrahedron Lett. *1972*, 5121.

[49] *T. Sasaki*, *S. Eguchi*, *T. Kiriyama*, and *Y. Sakito*, J. Org. Chem. *38*, 1648 (1973).

[50] *T. Saraie*, *T. Ishiguro*, *K. Kawashima*, and *K. Morita*, Tetrahedron Lett. *1973*, 2121.

[51] *G. Höfle*, Z. Naturforsch. *28b*, 831 (1973).

[52] *M. Makosza* and *I. Gajos*, Rocz. Chem., in press.

[53] *M. Makosza* and *A. Kacprowicz*, Rocz. Chem., in press.

[54] *M. Fedorynski* and *M. Makosza*, Bull. Acad. Pol. Sci. Ser. Sci. Chim., in press.

[55] *W. P. Weber* and *G. W. Gokel*, Tetrahedron Lett. *1972*, 1637.

[56] *W. P. Weber*, *G. W. Gokel*, and *I. K. Ugi*, Angew. Chem. *84*, 587 (1972); Angew. Chem. internat. Edit. *11*, 530 (1972).

[57] *E. V. Dehmlow* and co-workers, unpublished.

[58] *E. V. Dehmlow* and *G. C. Ezimora*, Tetrahedron Lett. *1970*, 4047; *1971*, 563, 1599.

[59] *M. Makosza* and *M. Fedorynski*, Bull. Acad. Pol. Sci. Ser. Sci. Chim. *19*, 105 (1971).

[60] *L. Skattebol*, *G. A. Abskharoun*, and *T. Greibrokk*, Tetrahedron Lett. *1973*, 1367.

[61] *M. Makosza* and *M. Fedorynski*, Synth. Commun. *1973*, 305.

[62] *P. Weyerstahl*, *G. Blume*, and *C. Müller*, Tetrahedron Lett. *1971*, 3869.

[63] *L. V. Chau* and *M. Schlosser*, Synthesis *1973*, 112.

[64] *P. Weyerstahl*, *R. Mathias*, and *G. Blume*, Tetrahedron Lett. *1973*, 611.

[65] *M. S. Newman* and *S. J. Gromelski*, J. Org. Chem. *37*, 3220 (1972).

[66] *M. S. Newman* and *Z. U. Din*, J. Org. Chem. *38*, 547 (1973).

[67] *M. S. Newman* and *W. C. Liang*, J. Org. Chem. *38*, 2438 (1973).

[68] *M. Makosza* and *M. Fedorynski*, Rocz. Chem. *46*, 533 (1972).

[69] *M. Makosza* and *I. Gajos*, Bull. Acad. Pol. Sci. Ser. Sci. Chim. *20*, 33 (1972).

[70] *M. Fedorynski* and *M. Makosza*, J. Organomet. Chem. *51*, 89 (1973).

[71] *D. Seyferth*, Accounts Chem. Res. *5*, 65 (1972).

[72] *H. K. Dietl* and *K. C. Brannock*, Tetrahedron Lett. *1973*, 1273.

[73] *M. Makosza*, *B. Serafinowa*, and *M. Jawdosiuk*, Rocz. Chem. *41*, 1037 (1967); *J. Lange* and *M. Makosza*, *ibid. 41*, 1303 (1967); *M. Makosza*, *B. Serafinowa*, and *T. Boleslawska*, *ibid. 42*, 817 (1968); *M. Makosza*, Tetrahedron Lett. *1969*, 673, 677; Rocz. Chem. *43*, 79, 334 (1969); *M. Makosza* and *M. Jawdosiuk*, Bull. Acad. Pol. Sci. Ser. Sci. Chim. *16*, 597 (1968).

[74] *M. Makosza*, *E. Bialecka*, and *M. Ludwikow*, Tetrahedron Lett. *1972*, 2391.

[75] *A. Jonczyk*, *B. Serafin*, and *M. Makosza*, Rocz. Chem. *45*, 1027, 2097 (1971); *M. Makosza*, *A. Jonczyk*, *B. Serafinowa*, and *Z. Mroczik*, *ibid. 47*, 77 (1973).

[76] *A. Jonczyk*, *B. Serafin*, and *M. Makosza*, Tetrahedron Lett. *1971*, 1351.

[77] *M. Makosza*, Tetrahedron Lett. *1966*, 4621.

[78] *M. Makosza*, Bull. Acad. Pol. Sci. Ser. Sci. Chim. *15*, 165 (1967).

[79] *M. Makosza* and *M. Fedorynski*, Rocz. Chem. *45*, 1861 (1971).

[80] *N. O. Vesterager*, *E. B. Pedersen*, and *S.-O. Lawesson*, Tetrahedron *29*, 321 (1973).

[81] *L. Dalgaard* and *S.-O. Lawesson*, Tetrahedron *28*, 2051 (1972).

[82] *R. A. Moss* and *F. G. Pilkiewicz*, Synthesis *1973*, 209.

[83] *B. Samuelsson* and *B. Lamm*, Acta Chem. Scand. *25*, 1555 (1971).

[84] *B. Cederlund* and *A.-B. Hörnfeldt*, Acta Chem. Scand. *25*, 3546 (1971); *B. Cederlund, A. Jesperson*, and *A.-B. Hörnfeldt, ibid. 25*, 3656 (1971).

[85] *K. Berg-Nielsen* and *E. Bernatek*, Acta Chem. Scand. *26*, 4130 (1972).

[86] *H. Ehrsson* and *A. Tilly*, Anal. Letters 6, 197 (1973).

[87] *M. Barreau* and *M. Julia*, Tetrahedron Lett. *1973*, 1537.

[88] *F. C. V. Larsson* and *S.-O. Lawesson*, Tetrahedron *28*, 5341 (1972).

[89] *A. Brändström* and *U. Junggren*, personal communication.

[90] *A. Jonczyk, M. Fedorynski*, and *M. Makosza*, Tetrahedron Lett. *1972*, 2395.

[91] *T. Greibrokk*, Acta Chem. Scand. *26*, 3305 (1972).

[92] *C. M. Starks* and *D. R. Napier*, Brit. Publ. Pat. Appl. 1227144 (1971).

[93] *W. P. Weber* and *J. P. Shephard*, Tetrahedron Lett. *1972*, 4907.

[94] *A. Brändström, U. Junggren*, and *B. Lamm*, Tetrahedron Lett. *1972*, 3173.

[95] *J. Solodar*, Tetrahedron Lett. *1971*, 287.

[96] *G. Märkl* and *A. Merz*, Synthesis *1973*, 295.

[97] *M. Makosza*, Tetrahedron Lett. *1966*, 5489.

[98] *M. Makosza* and *M. Jawdosiuk*, Bull. Acad. Pol. Sci. Ser. Sci. Chim. *16*, 589 (1968).

[99] *M. Makosza, B. Serafinowa*, and *I. Gajos*, Rocz. Chem. *43*, 671 (1969).

[100] Abstracts, Conference of Div. Organic Chemistry, Amer. Chem. Soc. Cape Cod, Mass. 1973; a) *M. Makosza*, p. 13; b) *D. Picker* and *A. W. Herriott*, p. 14.

[101] *J. Tsunetsugu, M. Sato*, and *S. Ebine*, J. C. S. Chem. Comm. *1973*, 363.

[102] *P. Stromquist, M. Radcliffe*, and *W. P. Weber*, Tetrahedron Lett. *1973*, 4523.

[103] *R. Mathias* and *P. Weyerstahl*, Angew. Chem. *86*, 42 (1974); Angew. Chem. internat. Edit. *13*, 132 (1974).

[104] *A. Jonczyk, B. Serafinowa*, and *J. Czyzewski*, Rocz. Chem. *47*, 529 (1973).

[105] *A. Jonczyk, M. Ludwikow*, and *M. Makosza*, Rocz. Chem. *47*, 89 (1973).

[106] *J. Dockx*, Synthesis *1973*, 441.

[107] *L. Dalgaard, H. Kolind-Andersen*, and *S.-O. Lawesson*, Tetrahedron *29*, 2077 (1973).

[108] *A. Merz*, Angew. Chem. 85, 868 (1973); Angew. Chem. internat. Edit. *12*, 846 (1973).

[109] *D. Landini, F. Montanari*, and *F. Rolla*, Synthesis *1974*, 37.

[110] *R. O. Hutchins* and *D. Kandasamy*, J. Amer. Chem. Soc. *95*, 6131 (1973).

[111] *A. Merz* and *G. Märkl*, Angew. Chem. 85, 867 (1973); Angew. Chem. internat. Edit. *12*, 845 (1973).

Photochemistry with Circularly Polarized Light

By Ole Buchardt[*]

The reactions induced by circularly polarized light are reviewed and a general discussion of the induction of optical activity by circularly polarized light is presented. It is concluded that three different mechanisms, or their combinations, can cause asymmetric induction. In each case the optical yield is dependent on the optical anisotropy factor g, the ratio between the circular dichroism ($\Delta\varepsilon$) and the extinction coefficient (ε). The results are discussed in terms of the presumed mechanisms, and particular attention is paid to the asymmetric synthesis of helicenes. It is concluded that this kind of photochemistry may have analytical importance.

1. Introduction

Introduction of optical activity into a chemical system without the use of any asymmetric chemical agent has attracted the attention of chemists for a long time, particularly in connection with the question of the origin of optical activity in living organisms[1-5].

Already in the pioneering paper of *Le Bel* in 1874[6] it was inferred that asymmetric induction could be caused by circularly polarized light, and the possibility was definitely stated by *van't Hoff* in 1894[7]. The detection of circular dichroism by *Cotton*[8] further corroborated that circularly polarized light could induce optical activity in chemical systems, and in the following years a number of papers appeared which described attempts to test the possibility. However, it was not until 1929 that such an attempt met with unequivocal success[9].

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2. How Can Asymmetric Induction with Circularly Polarized Light Occur?

The first condition to be met is that the light must be absorbed, since only light absorbed by a molecule can induce a photochemical reaction (Grotthus-Draper law)[*]. Secondly it is necessary to irradiate with light of such a wavelength that the circular dichroism is different from zero, or if broad band light is used, the integral of the circular dichroism over all wavelengths used must be different from zero.

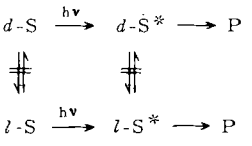
It is furthermore convenient to distinguish between three different mechanistic principles for asymmetric induction with circularly polarized light, namely:

1. Asymmetric destruction:
2. Partial photoresolution; and
3. Asymmetric synthesis[10].

[*] This does not in principle exclude a sensitized photochemical reaction where a chiral or prochiral molecule transfers energy to another prochiral molecule. However, so far no such mechanism has been proposed to explain asymmetric induction by circularly polarized light.

2.1. Asymmetric Destruction

In order to observe only asymmetric destruction we must have a substrate which consists of a racemic mixture whose enantiomers do not interconvert thermally or photochemically at the temperature at which the irradiation with circularly polarized light takes place. Furthermore, the substrate must undergo a photochemical reaction, *i.e.*



Irradiation with circularly polarized light of a wavelength where the circular dichroism is different from zero will excite more of one enantiomer than of the other (Cotton effect)[8, 12], thus

$$\frac{-\mathrm{d}[d\text{-S}]}{\mathrm{d}t} \neq \frac{-\mathrm{d}[l\text{-S}]}{\mathrm{d}t}$$

and after any time of irradiation and until there is no more substrate left, we will have different concentrations of *d*-S and *l*-S, and thereby an asymmetric destruction has been effected.

Obviously the optical yield[*] will be wavelength-dependent, and *Kuhn*[13] has shown that the observed rotation of the substrate after partial destruction is

$$\frac{g}{2} \times \mathrm{T} \times (1-\alpha) \ln \frac{1}{1-\alpha}$$

where α is the degree of destruction and T is the rotation which the total amount of substrate would have shown if it had been optically pure, and g is the optical anisotropy factor[14].

$$g = \frac{\varepsilon_L(d\text{-S}) - \varepsilon_R(d\text{-S})}{\varepsilon}$$

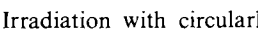
$\varepsilon_L(d\text{-S})$ and $\varepsilon_R(d\text{-S})$ are the extinction coefficients for the *d*-substrate with left and right circularly polarized light, respectively. Naturally

$$\varepsilon_L(d\text{-S}) = -\varepsilon_R(l\text{-S});\ \varepsilon_L(l\text{-S}) = -\varepsilon_R(d\text{-S})$$

Kuhn furthermore concluded that the maximal rotation would be equal to $g \times \mathrm{T} \times 0.184$, and that at a sufficiently high degree of photodestruction rather high optical purity of the remaining substance could be expected, *i.e.*, with $g = 0.04$, when 60% is left, the optical yield would be 1%; at 98.2% destruction 8%; at 99.995% destruction 20%; and if destruction is continued until only few molecules are left, quite high optical yields could be expected[13].

2.2. Partial Photoresolution

Partial photoresolution can take place in systems which undergo light-induced inversion, *i.e.*,



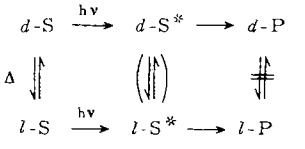
Again the wavelength must be such that the circular dichroism is not zero, and it can be shown that the maximum optical yield is:

$$\frac{|g|}{2} \times 100\%$$

2.3. Asymmetric Synthesis

Evidently there is a possibility that the products from asymmetric destruction themselves can be asymmetric and thus their formation would constitute what should be called an asymmetric synthesis, although, if such a reaction were completed, no asymmetric induction would be observed.

Otherwise an asymmetric synthesis can be expected in systems of the following kind, *i.e.*[*]



where there is a thermal equilibrium between the two enantiomeric conformations[**].

By irradiating with circularly polarized light of a wavelength for which the circular dichroism is not zero, differential excitation of the two enantiomers (*d*-S and *l*-S) will take place. If the relaxation to products is faster than a possible racemization in the excited state, and the products as indicated are chiral, an asymmetric synthesis has been performed.

The maximum optical yield can be calculated as

$$\left|\frac{\varepsilon_L(d\text{-S}) - \varepsilon_L(l\text{-S})}{\varepsilon_L(d\text{-S}) + \varepsilon_L(l\text{-S})}\right| = \left|\frac{\varepsilon_L(d\text{-S}) - \varepsilon_R(d\text{-S})}{\varepsilon_L(d\text{-S}) + \varepsilon_R(d\text{-S})}\right| = \frac{|\Delta\varepsilon|}{2\varepsilon}$$

or, expressed as a percentage,

$$\frac{|g|}{2} \times 100$$

From the above discussion it is apparent that the magnitude of the optical yield is dependent on g. Unfortunately g values are as a rule rather small; for strong absorption bands $g < 10^{-3}$, and even for weak absorption bands with a strong rotatory power, the g values are only expected to be of the order of magnitude of 10^{-2}[14].

3. Experimental Results

In most of the early work the source of optical rotation and the circularity of the light are not well defined and it is often difficult to understand why optical activity was observed. Furthermore, as the optical activity in several cases was marginally small, this makes it difficult to understand the mechanism, and the major emphasis has been placed on the most recent results in the following discussion.

[*] *d*-P and *l*-P only mean that the two products are enantiomers.

[**] It is interesting to note that virtually all but the very simplest molecules will exist in either enantiomeric conformations or enantiomeric states; *i.e.*, even a molecule like methane has conformations which are enantiomers and thus any notion that symmetric precursors should somehow be able to transfer "chirality of light" to give products in quantitative optical yield is unrealistic for this reason alone.

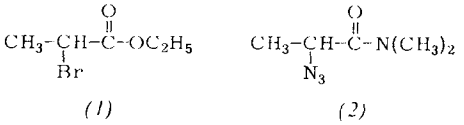
3.1. Asymmetric Destruction

As early as 1896 *Cotton*[8, 15] reported some unsuccessful attempts to destroy racemic salts of tartaric acid asymmetrically; similarly, an attempt to asymmetrically destroy, *inter alia*, racemic diazocamphor also met with failure[11].

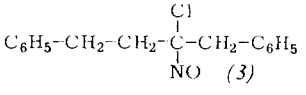
The first positive results were obtained by *Kuhn* and *Braun*[9] who successfully destroyed ethyl α-bromopropionate *(1)* with right and left circularly polarized light and obtained a low level of optical activity; the products from the photodestruction were not identified, and the source of the optical activity was not certain. However, *Kuhn* and *Knopf*[13, 16] shortly thereafter reported their elegant experiments with *N,N*-dimethyl-α-azidopropionamide *(2)*, which on irradiation with right or left circularly polarized light to 40% conversion gave mixtures with rotations at the sodium D-line of $+0.78°$ and $-1.04°$, respectively. The observed rotation is in good agreement with the *g*-factor of the substrate, which was calculated to be 0.02—0.03[14]. The signs of rotation are also in good agreement with theory[13, 16]. The products consisted of *N,N*-dimethylurea and an oily optically inactive, unidentified substance[13].

At the same time *Mitchell*[17] irradiated racemic "humulene nitrosite"[*] with right and left circularly polarized light, and obtained rotations ($\lambda = 546$ nm) of $+0.11°$ and $-0.09°$, respectively; however, the source of the rotation was not established[18]. In related experiments *Mitchell et al.* observed that 2-chloro-2-nitroso-1,4-diphenylbutane *(3)* became optically active upon irradiation to *ca.* 50% conversion[19]. Interestingly, these results have recently been repeated and found to be reproducible[20]. Marginal optical activity results on irradiation of the 4-(2-nitrophenyl)-1,4-dihydropyridine derivative *(4)* with circularly polarized light to give *(5)*[21].

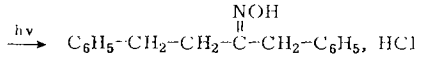
More recently, in connection with an attempt to undertake an absolute asymmetric synthesis, it was reported that asymmetric destruction of the 2-cyclopentenone dimer *(6)* could be effected with circularly polarized light[22]. It has also been shown that racemic hexahelicene undergoes asymmetric destruction, with formation of unknown products[23] (see Section 3.3).

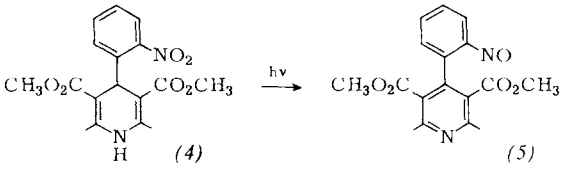


(1) *(2)*

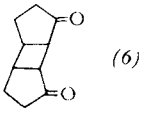


(3)





(4) *(5)*



(6)

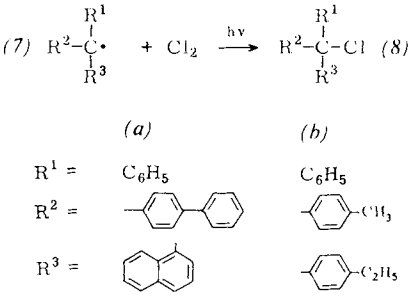
[*] Product of uncertain structure formed on addition of N_2O_3 to the sesquiterpene humulene.

3.2. Partial Photoresolution

So far only a rather limited amount of work has been done, but the results appear to be encouraging enough to merit further exploration. *Stevenson et al.*[24, 25] found that aqueous solutions of racemic trioxalatochromate(III), di-μ-hydroxo-bis[dioxalatochromate(III)], and *cis*-dioxalatodiaquochromate(III) upon irradiation with circularly polarized light were partially resolved into their enantiomers. It was also shown that *trans*-dioxalatodiaquochromate(III) became optically active under the same conditions; this is presumably due to its light-induced isomerization to the *cis*-form, which is then partially resolved by circularly polarized light. This was independently corroborated by other workers who irradiated potassium trioxalatochromate(III) ($g = 0.04$) with circularly polarized light and also obtained photoresolution[26]. In a closely related experiment *Stevenson*[27] demonstrated the applicability of this method in a partial photoresolution of tris(2,4-pentanedionato)chromium(III).

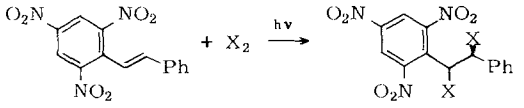
3.3. Asymmetric Synthesis

The chemical literature contains several reports of absolute asymmetric synthesis with circularly polarized light. However, in all the early work the rotations were marginal and the source of optical activity not well established. The first reports to claim a successful asymmetric synthesis were those of *Karagunis* and *Drikos*[28, 29]. They stated that irradiation of mixtures of chlorine and triarylmethyl radicals *(7)* with circularly polarized light resulted in the generation of optical activity, which they ascribed to an asymmetric synthesis of the triarylmethyl chloride *(8)*. The source of optical activity was not identified and, in view of the very complex character of the reaction mixture, it is difficult to understand the details of these results.

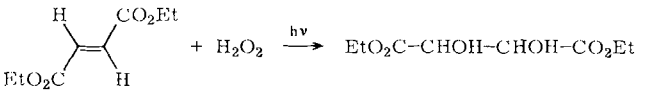


The results of *Davis et al.*[30, 31] also appear rather puzzling. They found that irradiation of mixtures of bromine and 2,4,6-trinitrostilbene *(9)* led to a light-induced addition of bromine to the double bond. After irradiation with circularly polarized light, marginal optical activity of the reaction mixture could be observed[30]. Similar results were described for chlorine and trinitrostilbene[31]. In this case also, the source of the optical activity was not identified, and it is noteworthy that a later attempt to reproduce the results failed[20].

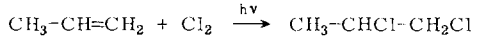
Ten years later *Davis et al.*[32] reported that irradiation of a mixture of diethyl fumarate *(10)* and hydrogen peroxide with circularly polarized light resulted in the formation of



(9) X = Cl, Br

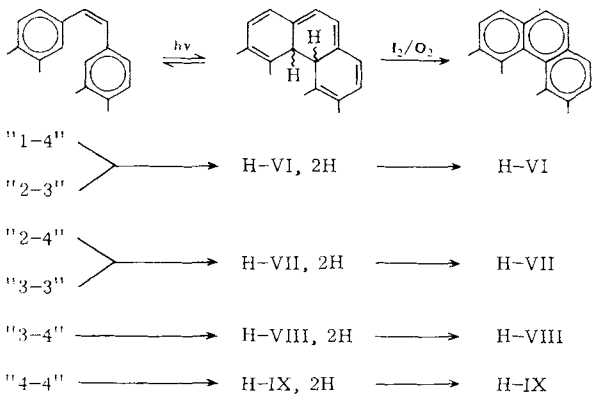


(10) *(11)*



optically active diethyl tartrate. However, the source of optical activity was not definitely determined. These results have also proved to be non-reproducible[22]; not only were later workers unable to measure any optical activity, but they even failed to detect any diethyl tartrate by gas chromatography.

Recently two independent attempts to synthesize helicenes asymmetrically with circularly polarized light have been undertaken. It was found that if the previously described[34] light-induced formation of helicene[*] from either 1-phenyl-2-(2-benzo[c]phenanthryl)ethylene ("1—4")[*] or 1-(2-naphthyl)-2-(3-phenanthryl)ethylene ("2—3") was carried out with circularly polarized light, optically active hexahelicene was formed[23, 35, 36]. Similarly, it was shown that optically active



Scheme 1. Principle of light-induced helicene synthesis, after [34].

Table 1. Asymmetric synthesis of helicenes with circularly polarized light.

Substrate [a]	Product	Wavelength of excitation [nm]	Circularity of light [b] [%]	Observed rotation [c] [°]	Optical yield [d] [%]	Ref. [e]
"1-4"	Hexahelicene	370±6	R, 89	− 8.0±0.8	0.06	[23, 36, 46]
			L, 89	+ 7.6±0.9		
o-F-"1-4"	4-Fluorohexahelicene	370±6	R, 89	−31.5±1.2	0.23	[38, 46]
			L, 89	+34.0±1.3		
o-Cl-"1-4"	4-Chlorohexahelicene	370±6	R, 89	−45.8±1.4	0.33	[38]
			L, 89	+46.9±2.0		
o-Br-"1-4"	4-Bromohexahelicene	370±6	R, 89	−38.7±1.4	0.26	[38]
			L, 89	+34.2±2.4		
o-CH_3-"1-4"	4-Methylhexahelicene	370±6	R, 89	−35.6±1.0	0.26	[38]
			L, 89	+35.9±1.1		
p-F-"1-4"	2-Fluorohexahelicene	370±6	R, 89	−10.5±0.9	0.08	[38, 46]
			L, 89	+10.7±0.9		
p-Cl-"1-4"	2-Chlorohexahelicene	370±6	R, 89	−16.5±0.8	0.12	[38]
			L, 89	+15.8±0.8		
p-Br-"1-4"	2-Bromohexahelicene	370±6	R, 89	−23.8±0.9	0.17	[38]
			L, 89	+23.2±0.9		
p-CH_3-"1-4"	2-Methylhexahelicene	370±6	R, 89	−36.4±1.0	0.26	[38]
			L, 89	+37.5±1.1		
"2-3"	Hexahelicene	370±6	R, 89	—	0.3	[23, 36, 46]
			L, 89	+36.1±2		[57]
"2-4"	Heptahelicene	370±6	R, 89	−	0.74±0.06	
			L, 89	+	0.76±0.06	[36, 38]
		400±6	R, 89	−	1.29±0.06	
			L, 89	+	1.26±0.06	
"3-3"	Heptahelicene	370±6	R, 89	−	0.57±0.06	[38]
			L, 89	+	0.62±0.06	
"3-4"	Octahelicene	370±6	L, 75	+	1.77	[36, 37]
		410±6	L, 75	+	2.00	
"4-4"	Nonahelicene	370±6	L, 89	+30.5		[37, 57]
"3-2-3"	Nonahelicene	370±6	L, 89	+		[57]
			R, 89	−		

[a] Toluene solutions (benzene for "4-4").
[b] R = right, L = left circularly polarized light.
[c] To indicate the error of the observations.
[d] Estimated by comparison with hexahelicene (except for hexahelicene itself).
[e] Numbers taken from the first reference.

A related attempt to generate optically active 1,2-dichloropropane by the light-induced reaction of propene with chlorine using circularly polarized light was also reported to be successful[33]. A later attempt to reproduce this failed to reveal any optical activity[22].

[*] For simplicity, the helicenes for which there are no definitive IUPAC nomenclature rules will here be designated as follows: hexahelicene = H-VI; octahelicene = H-VIII; 2-fluorohexahelicene = 2-F-H-VI, *etc.* The precursors are symbolized by the number of benzene rings already present: 1-phenyl-2-(2-benzo[*c*]phenanthryl)ethylene = "1-4"; 1-(4-fluorophenyl)-2-(benzo[*c*]-phenanthryl)ethylene = *p*-F-"1-4", *etc.*

hepta- (H-VII), octa- (H-VIII), and nonahelicene (H-IX) could be generated by irradiation of the corresponding diarylethylenes with circularly polarized light[36-38] (Scheme 1).

In each case both right and left circularly polarized light was used, and it was found that in the wavelength regions employed, *i.e.*, 290—370 nm[23,27], 340—400 nm[36], and 370 ± 6 nm[38], right circularly polarized light led to a product with a negative rotation, whereas left circularly polarized light gave a positive rotation (measured at 589 and 436 nm, Table 1).

A priori, the observed asymmetric induction could be caused by any one of the three previously discussed mechanisms (Section 2), or combinations thereof. Thus asymmetric destruction of the helicenes appeared to be a possibility, and since the primary light-induced reaction which leads to dihydrohelicenes is photoreversible, the optical activity could also be due to a partial photoresolution at this stage[23,37]. The oxidation to helicenes is believed to be thermal[39-42].

However, the fact that this reaction also has the potential for an asymmetric synthesis was one of the main reasons for studying it[43]. From Scheme 2 it is seen that the diarylethylenes, *e.g.*, the "1-4" precursor, form mixtures of equal amounts of enantiomeric conformers which can thermally racemize by either of the two pathways shown.

In order to shed more light on the mechanism, two types of experiments were performed:

a) It was attempted to destroy hexahelicenes asymmetrically under circumstances where asymmetric induction was observed with the diarylethylenes; however, no optical activity was observed. Furthermore, in the case of asymmetrical destruction rotations opposite to those found would be expected[23,36]. However, on prolonged irradiation of racemic helicenes with circularly polarized light, asymmetric destruction did in fact take place, and rotations opposite to those of the original experiments were found[23].

b) The wavelength dependency of the optical yield was examined for some of the helicene precursors (Fig. 1)[36,38].

Finally, a valid mechanism should be able to explain why the "1-4" substrate only gives a fraction of the optical yield which is found in the case of the "2-3" precursor (Table 1).

The first mechanism (asymmetric destruction) can be discarded: (a) Since no optical activity could be observed with the pure helicenes under otherwise similar conditions; (b) because of the sign of rotation; (c) since the optical yield as a function of wavelength is not proportional to the *g*-factor (as shown for octahelicene in Fig. 1); (d) because this

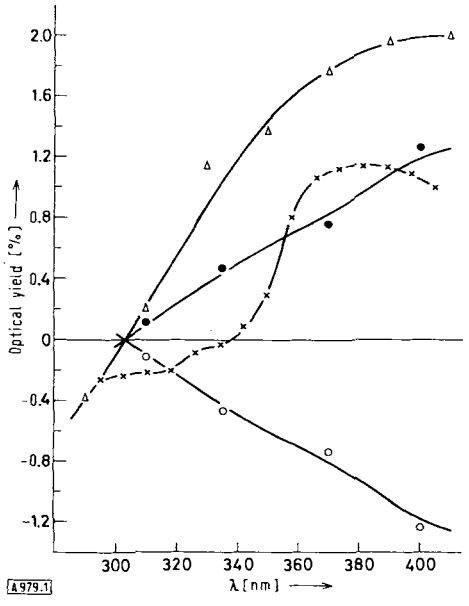
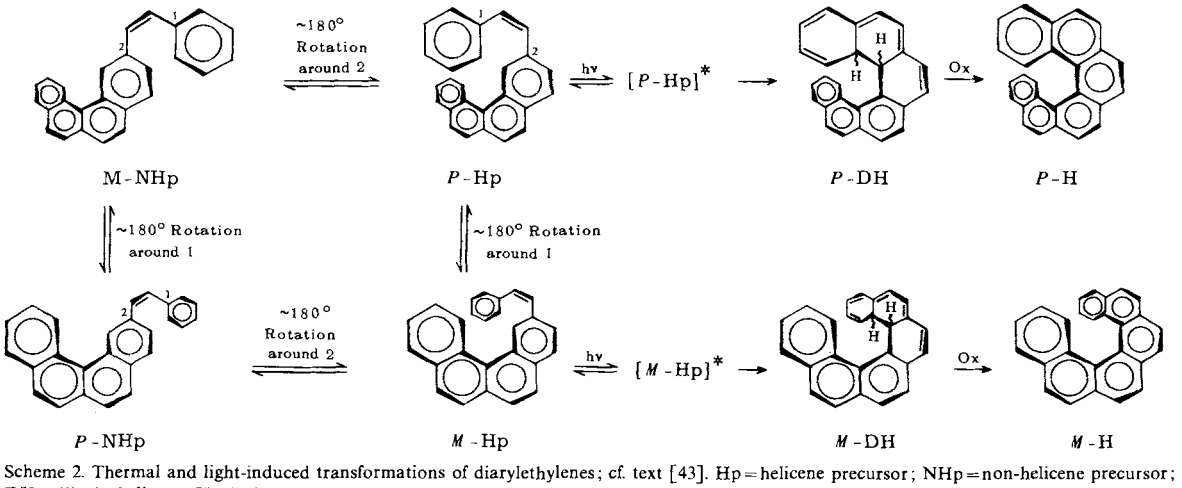


Fig. 1. Wavelength dependence of the optical yield for: ●, "2-4" irradiated with left circularly polarized light; ○, "2-4" irradiated with right circularly polarized light; △, "3-4" irradiated with left circularly polarized light; ×, "*g*" of octahelicene.

mechanism cannot explain the difference in optical yield of hexahelicene from the "1-4" *versus* the "2-3" precursor (Table 1).

The second mechanism (partial photoresolution) can be discarded because: (a) The literature indicates that the oxidation of dihydrohelicenes is too fast[39,40]; (b) because the optical yield curves (Fig. 1) which reflect the *g*-values of the substrates, *i.e.*, the dihydrohelicenes, would be expected to be different[36,38]; (c) this mechanism could not easily explain the difference in optical yield from the "1-4" *versus* the "2-3" precursor.

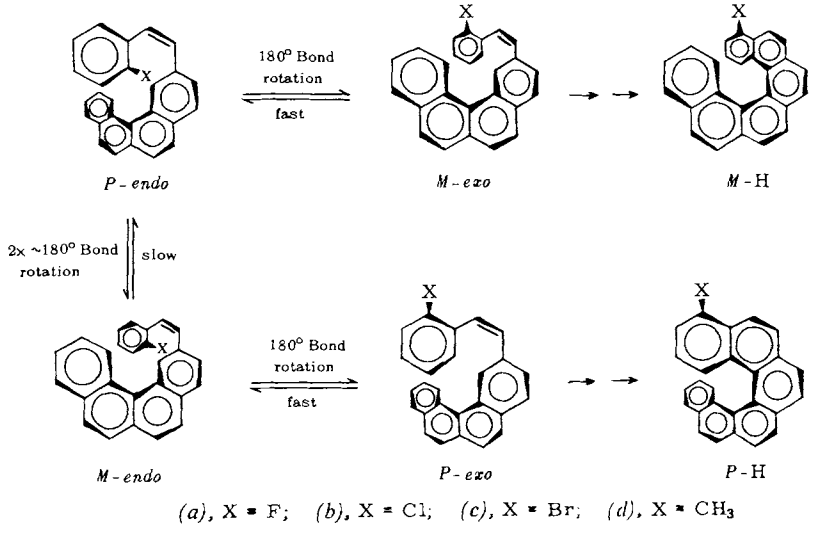
We can thus conclude that the mechanism responsible for the asymmetric induction is the asymmetric synthesis, which fits the experimental results in a satisfactory manner: (a) The



Scheme 2. Thermal and light-induced transformations of diarylethylenes; cf. text [43]. Hp = helicene precursor; NHp = non-helicene precursor; DH = dihydrohelicene; H = helicene.

sign of the rotation is correct; (b) the optical yield curves follow the expected g-curves for the substrates, cf. ref.[36]; (c) the difference in optical yield for the "1-4" *versus* the "2-3" precursor can be explained as follows: From Scheme 2 it can be seen that in the "1-4" precursor it only takes a rotation of $\approx 180°$ about the phenyl-ethylene bond to interchange the enantiomers, whereas racemization in the "2-3" precursor is believed to be a process requiring more energy. It was therefore proposed that some racemization could take place in the excited singlet state of "1-4", which is presumably responsible for the ring closure[40], whereas this is not the case for the "2-3" precursor. The more trivial explanation that the difference was due to different g-values of the two precursors was not excluded[36].

A solution of this problem was attempted by irradiating a series of *ortho*-substituted "1-4" precursors (Table 1; Scheme 3).



Scheme 3. Transformations of *ortho*-substituted "1-4" hexahelicene precursors.

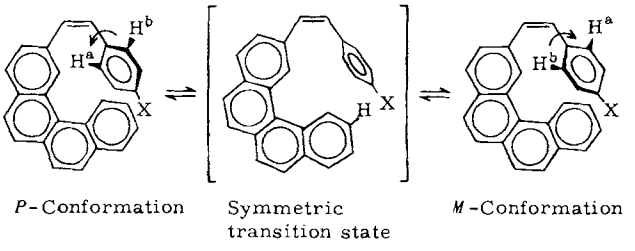
It seems reasonable to assume that the substituent does not contribute significantly to the electronic structure of the molecule. Therefore it is expected that both the *endo* and *exo* forms will have nearly the same circular dichroism and absorption spectra as the unsubstituted compound.

From Scheme 3 it is seen that closure to the helicenes can only take place from the *exo*-conformations and that rotation of $\approx 180°$ about the phenyl-ethylene bond will interchange the *M-endo* form with the *P-exo* form, *etc.*

This means that racemization by a simple $\approx 180°$ rotation is no longer possible, and if, as expected, the majority of the substrate molecules exist as the *exo*-enantiomers, the optical yield from these compounds will be of the same order of magnitude as that from the "2-3" precursor[44,45]. The results, listed in Table 1, are in excellent agreement with the bond-rotation hypothesis, *i.e.*, that the difference in optical yield from "1-4" *vs.* "2-3" is due to racemization in the excited state of the "1-4" precursor[38,46].

The corresponding *para*-substituted "1-4" precursors were also irradiated with circularly polarized light, and, *a priori*, it was expected that they would behave like the unsubstituted "1-4" precursor. As can be seen from Table 1, this is not the case; the optical yield increases with increasing size of the substituent[38]

An explanation for this was found by inspection of molecular models, where it is seen that the *para*-substituent in the phenyl group interacts sterically with the hydrogen in the 11-position of the benzo[*c*]phenanthryl group in the transition state for racemization (Scheme 4). Thus, as the *para*-substituent increases in size, the activation energy for racemization could



Scheme 4. Racemization of *para*-substituted "1-4" hexahelicene precursors.

be expected to increase (Fig. 2), thereby prohibiting the racemization in the excited state.

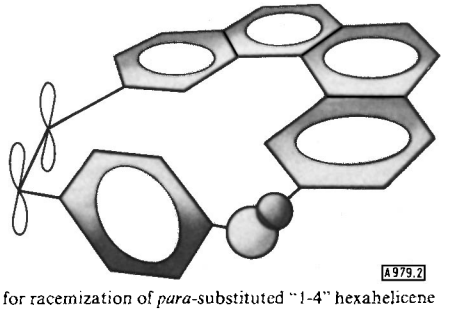


Fig. 2. Transition state for racemization of *para*-substituted "1-4" hexahelicene precursors.

Finally it should be mentioned that when 1-phenyl-2-(2-hexahelicenyl)ethylene is irradiated with circularly polarized light to complete disappearance, the octahelicene formed is optically inactive, but if the reaction is stopped before that, the octahelicene has a small but significant rotation[37].

4. Miscellaneous Results

Besides the literature quoted and discussed so far, there are several reports of fruitless attempts to induce optical activity with circularly polarized light. Some examples of these are:

Light-induced decarboxylation of α-methyl-α-cyanobutyric acid and α-methyl-α,β-dichlorosuccinic acid[47]; utilization of the Ciamician reaction of nitroaromatics in an asymmetric transformation of 2-nitrobenzaldehyde dipentyl acetal with circularly polarized light to pentyl 2-nitrosobenzoate[48]: addition of bromine to angelic acid[49]; preparation of the hydrogen sulfite adduct of acetaldehyde during irradiation with circularly polarized light[50].

Some positive results which apparently never have been explained are that the rate of mutarotation of a sugar was dependent on whether irradiation took place with right or left circularly polarized light[51]. The irradiation of photographic material with circularly polarized light led to the formation of optically active substances[52].

Furthermore, there have been attempts to utilize the combination of a magnetic field with photochemistry to induce optical activity, cf. ref.[53][*]; and attempts to show that circular polarization of *Bremsstrahlung* (γ-rays) can cause asymmetric induction have been reported[5, 55, 56].

5. Conclusion

Although photochemistry with circularly polarized light has been a subject of study for many years, it appears to be a promising area for further investigation. It seems reasonable to expect that new systems that will give asymmetric induction by irradiation with circularly polarized light can be found, in spite of the fact that few positive results have so far been reported.

Photochemistry with circularly polarized light using selected substrates permits a partial optical resolution or destruction which may be of interest in some cases. Of more importance may be the possibility of obtaining CD spectra of otherwise unresolvable (conformeric) enantiomers as well as new information about the chemistry of excited states.

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[*] As a result of the Faraday effect, the passage of plane polarized light through a medium placed in a magnetic field whose direction is parallel to the direction of the light will cause either magnetic optical rotatory dispersion (MORD) or, if the light corresponds to an absorption band of the substrate, magnetic circular dichroism (MCD) [12]. Thus, in principle, optical activity can be induced by circularly polarizing the light in the medium, cf. refs. [53—54].

[1] For a most comprehensive recent treatment of all aspects of asymmetric synthesis, see *J. D. Morrison* and *H. S. Mosher*: Asymmetric Organic Reactions. Prentice-Hall, London 1971.

[2] *A. I. Oparin*: Origin of Life. 3rd Edit. Academic Press, New York 1957.

[3] *J. Keosian*: The Origin of Life, 2nd Edit., Reinhold, New York 1968.

[4] *G. Wald*, Ann. N. Y. Acad. Sci. 69, 352 (1967).

[5] *A. S. Garay*, Nature (London) *219*, 338 (1968).

[6] *Le Bel*, Bull. Soc. Chim. Fr. *22*, 347 (1874).

[7] *J. H. van't Hoff*: Die Lagerung der Atome in Raume. 2nd Edit. Vieweg, Braunschweig 1894, p. 30.

[8] *A. Cotton*, Ann. Chim. Phys. [7] *(8)*, 347 (1896).

[9] *W. Kuhn* and *F. Braun*, Naturwissenschaften *17*, 227 (1929).

[10] This is often referred to as "absolute asymmetric synthesis", apparently after ref. [11].

[11] *G. Bredig*, *P. Mangold*, and *T. G. Williams*, Angew. Chem. *36*, 456 (1923).

[12] See, *e.g.*, *P. Crabbé*: An Introduction to the Chiroptical Methods in Chemistry. Syntex, S. A. and Universidad Nacional Autonoma de Mexico, Mexico 1971.

[13] *W. Kuhn* and *E. Knopf*, Z. Phys. Chem. *7 B*, 292 (1930).

[14] *W. Kuhn*, Trans. Faraday Soc. *26*, 293 (1930).

[15] *A. Cotton*, J. Chim. Phys. *7*, 81 (1909).

[16] *W. Kuhn* and *E. Knopf*, Naturwissenschaften *18*, 183 (1930).

[17] *S. Mitchell*, J. Chem. Soc. *1930*, 1829.

[18] *S. Mitchell*: The Cotton Effect and Related Phenomena. Bell, London 1933.

[19] *S. Mitchell* and *I. M. Dawson*, J. Chem. Soc. *1944*, 452.

[20] *M. Rasmussen* and *I. Scott*, personal communication.

[21] *J. A. Berson* and *E. Brown*, J. Amer. Chem. Soc. *77*, 450 (1955).

[22] *P. Boldt*, *W. Thielecke*, and *H. Luthe*, Chem. Ber. *104*, 353 (1971).

[23] *A. Moradpour*, *J. F. Nicoud*, *G. Balavoine*, *H. Kagan*, and *G. Tsoucaris*, J. Amer. Chem. Soc. *93*, 2353 (1971).

[24] *K. L. Stevenson* and *J. F. Verdieck*, J. Amer. Chem. Soc. *90*, 2974 (1968).

[25] *K. L. Stevenson* and *J. F. Verdieck*, Mol. Photochem. *1*, 271 (1969).

[26] *B. Norden*, Acta Chem. Scand. *24*, 349 (1970).

[27] *K. L. Stevenson*, J. Amer. Chem. Soc. *94*, 6652 (1972).

[28] *G. Karagunis* and *G. Drikos*, Naturwissenschaften *21*, 607 (1933); Nature (London) *132*, 354 (1933).

[29] *G. Karagunis* and *G. Drikos*, Z. Phys. Chem. *26 B*, 428 (1934).

[30] *T. L. Davis* and *R. Heggie*, J. Amer. Chem. Soc. *57*, 377 (1935).

[31] *T. L. Davis* and *R. Heggie*, J. Amer. Chem. Soc. *57*, 1622 (1935).

[32] *T. L. Davis* and *J. Ackerman, Jr.*, J. Amer. Chem. Soc. *67*, 486 (1945).

[33] *M. Betti* and *E. Lucchi*, Atti X° Congr. Int. Chim. *2*, 112 (1938); Chem. Abstr. *33*, 7273 (1939).

[34] *M. Flammang-Barbieux*, *J. Nasielsky*, and *R. H. Martin*, Tetrahedron Lett. *1967*, 743; *R. H. Martin*, *M. Flammang-Barbieux*, *J. P. Cosyn*, and *M. Gelbeke*, *ibid. 1968*, 3705.

[35] *G. Tsoucaris*, *G. Balavoine*, *A. Moradpour*, *J. F. Nicoud*, and *H. Kagan*, C. R. Acad. Sci. Paris *272*, 1271 (1971).

[36] *W. J. Bernstein*, *M. Calvin*, and *O. Buchardt*, J. Amer. Chem. Soc. *94*, 494 (1972).

[37] *H. Kagan*, *A. Moradpour*, *J. F. Nicoud*, *G. Balavoine*, *R. H. Martin*, and *J. P. Cosyn*, Tetrahedron Lett. *1971*, 2479.

[38] *W. J. Bernstein*, *M. Calvin*, and *O. Buchardt*, J. Amer. Chem. Soc. *95*, 527 (1973).

[39] The dihydrohelicenes have never been observed; however, as a rule these dihydroaromatics seem to undergo a sufficiently fast thermal oxidation to prohibit any build-up under the conditions which were employed in the experiments with circularly polarized light, cf. refs. [38—40].

[40] *K. A. Muszkat* and *E. Fischer*, J. Chem. Soc. *B 1967*, 662.

[41] *M. Kaganowich*, *G. Fischer*, and *E. Fischer*, Z. Phys. Chem. *76*, 79 (1971).

[42] *T. Knittel-Wismonsky*, *G. Fischer*, and *E. Fischer*, Tetrahedron Lett. *1972*, 2853.

[43] In this nomenclature *P* and *M* denote right and left handed helical conformations, respectively. See *R. S. Cahn*, *C. K. Ingold*, and *V. Prelog*, Angew. Chem. *78*, 413 (1966); Angew. Chem. internat. Edit. *5*, 385 (1966).

[44] The fact that partially resolved 2-bromohexahelicene with $[\alpha]_{589}^{20} = -444°$ can be converted to hexahelicene with $[\alpha]_{589}^{20} = -420°$ by reduction with butyllithium in hexane indicates that the substituted helicenes have very nearly the same rotations as the parent compound. The optical yields given here are calculated on the basis of the assumption that the rotations of hexahelicene and its derivatives are equal, see ref. [45].

[45] *D. A. Lightner*, *D. T. Hefelinger*, *T. W. Powers*, *O. W. Frank*, and *K. N. Trueblood*, J. Amer. Chem. Soc. *94*, 3492 (1972).

[46] *W. J. Bernstein*, *M. Calvin*, and *O. Buchardt*, Tetrahedron Lett. *1972*, 2195.

[47] *F. Henle* and *H. Haakh*, Ber. Deut. Chem. Ges. *41*, 4261 (1908).

[48] *M. Freundler*, Bull. Soc. Chim. Fr. [4] *1*, 657 (1907); Ber. Deut. Chem. Ges. *42*, 233 (1909).

[49] *M. Padoa*, Gazz. Chim. Ital. *41*, 469 (1911).

[50] *J. Pirak*, Biochem. Z. *130*, 76 (1922).

[51] *M. P. Souty*, C. R. Acad. Sci. Paris *199*, 198 (1934).

[52] *H. Zocher* and *K. Coper*, Z. Phys. Chem. *132*, 313 (1928); *J. C. Ghosh*, J. Indian Chem. Soc. *16*, 51 (1939).

[53] *P. Curie*, J. Phys. Radium *3*, 409 (1894); *D. Radulescu* and *V. Moga*, Bull. Soc. Chim. Romania *1*, 18 (1939); Chem. Abstr. *37*, 4070 (1943).

[54] *E. U. Condon* and *H. Odishaw*: Handbook of Physics. McGraw-Hill, New York 1958.

[55] *F. Vester*, *T. L. V. Ulbricht*, and *H. Krauch*, Naturwissenschaften *46*, 68 (1959).

[56] *T. L. V. Ulbricht*, Quart. Rev. Chem. Soc. *13*, 48 (1959).

[57] *O. Buchardt* and *N. Friedman*, unpublished results.

Recent Discoveries in the Evolution of Proteins

By Roger Acher[*]

Is it possible to reconcile the great diversity of present-day proteins with a unitary theory of the evolution of these molecules? The mechanisms of diversification of proteins are undoubtedly not yet all known, but it is clear that the linear construction of polypeptide chains lends itself to operations such as addition, insertion, deletion, and fusion. Combinations of these modifications would explain the development of an infinite number of entirely different proteins from one ancestral molecule.

1. Introduction

If it is accepted that proteins are the second reflection of genes by the double mechanism of the transcription of deoxyribonucleic acids into messenger ribonucleic acids and the translation of the latter into polypeptide chains[1], the variation of their amino-acid sequence can give us a fairly faithful picture of the events that affect or have affected the genes. The neo-Darwinian theory of evolution assumes that genes have been modified in the course of time by mutations similar to those that can be observed today, *i. e.* by random minor mutations, and that natural selection has led to evolutionary lines. This theory accounts for the fact that the variation of organisms, as revealed by paleontology, is diffuse in its endeavors and yet progressive in its results, the most recent species being the most highly adapted. The observations on which this view is based are thus essentially morphological. It must be pointed out that while natural selection does not act equally on all the organs, but acts, for example, at one time on the organs of locomotion and at another on the respiratory organs, *etc.*, and so leads to inequalities in the evolutionary rhythms of these organs, coordination must have existed between the individual evolutions of the various parts to lead to animals as highly organized as mammals and birds.

The evolution of molecules, *i. e.* of genes and consequently of proteins, presents no new theoretical problems with regard to the evolution of organisms if one accepts the Darwinian view. The combination of mutation and selection can also be invoked here, and the provision of a chain of enzymes to ensure regulated biosynthesis of histidine presents no more difficulty than *e. g.* the integration of specialized elements leading to an eye having the property of accommodation. On the other hand, the theory also has its weaknesses, such as the arbitrary choice of the organ or of the molecule designated to play a predominant role in the future, the fact that the advantage of the initial mutation is too small for selection to seize upon, the difficulty of explaining the coordination of the various individual evolutions, *etc.*

The question has been raised whether proteins really evolve, *i. e.* pass through structures increasingly efficient on the biological level, or whether the action of selection stops on the morphological plane (the deoxyribonucleic acids constituting the genes evolve them by definition). In this case the substitutions observed in the proteins from one species to another would have no evolutionary significance. It seems difficult to accept that evolution has been quantitative only at the level of the proteins and qualitative at the anatomical level. On the other hand, the number of different proteins present in a mammal is considerably greater than that found in a bacterium[2], and cellular differentiation must have led to multiplication and specialization of the proteins.

A special difficulty in the study of the evolution of proteins is that whereas an organ more or less expresses its function in its form and thus permits comparative evaluation from one species to another, this is not so for a molecule, even in the fairly rare cases in which its three-dimensional structure is known. The conformation of a protein is not functionally intelligible by itself. The "biological" function of a protein is determined by its ability to associate with other molecules, *i. e.* to participate in specific interactions. In these interactions, the morphology of the protein on the one hand and the nature of the exposed chemical groups on the other are fundamental, since the first of these factors determines the possibility of contact and the second the possibility of bonding. Since the soluble proteins are more or less globular macromolecules, it is clear that some of the residues will be buried and will not intervene directly in external interactions; on the other hand, these residues take part in interactions within the globule, so ensuring its stability. The constraints that evolution can exert on the protein will differ according to whether the residues concerned are on the surface or buried, and the three-dimensional structure of the protein must therefore be known for an interpretation of the substitutions. The conformation of the molecules that react with the protein (substrates, receptors, antigens, *etc.*) must also be known, since natural selection acts on the function that results from the interaction. Insofar as biological properties cannot yet be translated on the atomic level, the meaning of amino-acid substitutions is still difficult to perceive. One is usually reduced to taking stock of the structural variations of the proteins in the hope of learning closer details of the action mechanisms.

It is clear that one can only study the proteins of species that are now living, *i. e.* species at the ends of their evolutionary lines. One can postulate that the physiological functions, and consequently the proteins involved in them, have evolved with rhythms very roughly parallel to that of the evolution of the general morphology. In this case the proteins of existing lower species could be regarded as relatively close to the ancestral proteins. It is possible to verify this assumption by examining species that are morphologically similar, but for which paleontology indicates that they belong to lines that diverged a long time ago.

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For example, the primitive bony fish *Polypterus bichir* belongs to the line of Polypteriforms, which separated about 300 million years ago from the line of the Actinopterygians (modern bony fish)[4]. Nevertheless, it possesses the same neurohypophyseal hormones as the latter, whereas mammals and birds, which branched off at roughly the same period, have different neurohypophyseal hormones. Further examples are necessary, however, before the parallelism of the morphological and molecular evolutions can be broadly accepted.

Great progress has been made in recent years in the purification and sequence analysis of proteins, and the number and size of the known proteins have considerably increased since 1966[5]. Automated determinations of amino-acid sequences will considerably increase the volume of the "Atlas of Protein Sequence and Structure"[6], whose contents are already doubling annually. The number of living species is probably of the order 5—10 million[7], and if each species is assumed to possess its own specific proteins, with a purely arbitrary average of 100000 proteins per species, there must be 500 to 1000 billion proteins to try the endurance of biochemists and their instruments. However, progress in the determination of sequences will tell us little about the relations that exist between structure and biological activity until similar progress has been achieved in the study of conformations.

Insofar as all hereditary variations known at present are mutations, and evolution by definition implies changes in the genetic material, the current "mutations" of proteins are particularly valuable for the elucidation of the mechanisms that might have been involved in their evolution. This progress report will therefore examine the different types of structural variations shown both by molecular genetics and by comparative biochemistry with the aid of selected examples.

While classification of biological species is relatively easy, the same cannot be said of the classification of molecular species. The sequence of each protein is assumed to be determined by a structural gene, which itself consists of a sequence of deoxyribonucleotides. The fate of this structural gene is to some extent independent of the fate of the biological species. The formation of a new biological species from an old one (speciation) can take place without modification of the structural gene. Conversely, the structural gene may be duplicated and give two lines of proteins without the formation of two new biological species. A protein is recognized primarily by its biological function; isolation of the proteins of different species on the basis of this criterion gives a family of "homologous" proteins that have structural similarities among themselves. When several proteins apparently having the same function but differing from one another in their amino-acid sequences ("isologous" proteins) are found in a single species ("polymorphism"), each of these proteins is assumed to correspond to a separate structural gene; in this case, particularly if polymorphism is not general to all the species compared, it may become difficult to pick out the lines of homologous proteins among the isologous proteins. In a given biological species, moreover, proteins having different functions may show structural similarities that lead one to assume that the structural genes must have been derived from a common ancestral gene by duplication and mutation. The structural analogies are less pronounced in this case than in the case of isologous proteins. These chemically similar but functionally different proteins could be referred to as "analogous" proteins.

2. Families of Homologous Proteins

A number of cases are known in which the protein is recognizable on the ladder of vertebrates both by its function and by certain structural elements. Paleontology has shown that the vertebrates developed during the last 500 million years, so that the variations of their proteins extend over a sufficiently long time to reveal general trends. The families that now offer a range extending from the lower vertebrates to the mammals are still limited in number: cytochrome c, the α and β chains of hemoglobin, fibrinopeptides, and neurohypophyseal hormones. The observations gathered so far indicate that there is little variation in the length of the polypeptide chain, and that the most common type of modification is the substitution of amino-acid residues. The substitution of an amino acid can be brought about by the substitution of a single base in the triplet of nucleotides that codes each residue at the gene level (point mutation), and this explains why the phenomenon is so frequent.

2.1. Substitutions of Amino Acids

Comparison of the sequences of the proteins of a single family shows that certain positions are immutable, while others are substituted with various frequencies. The substitutions must not affect the general conformation of the molecule, which determines its function. It is therefore interesting to examine first the reasons for the invariability of certain positions of the polypeptide chain.

2.1.1. The Functional Invariability of Hydrophobic Residues

Through the crystallographic study of three-dimensional structures it has been possible in certain cases to localize, in space, the immutable positions in a family of proteins and to interpret the constraint in terms of the requirements of conformational stability.

2.1.1.1. Cytochrome c

Cytochrome c is an electron-transporting protein found in the mitochondria of aerobic organisms. Regardless of its source, the molecule always consists of a single polypeptide chain of 104 to 112 residues covalently bonded to the same prosthetic group. The iron atom is bivalent or trivalent, according to whether the cytochrome c reacts with cytochrome reductase or with cytochrome oxidase. This dual interaction should necessitate a fairly rigorously defined conformation. Since the cytochromes c of all the species studied react in a similar manner with beef cytochrome oxidase, we may therefore expect to find a close conformational relationship between them. This is fully confirmed by X-ray analysis of horse and bonito ferricytochromes c[8]. In vertebrates the chain always contains 104 residues, with an acetylated N-terminal group, while it is extended to 108 residues in insects, 108 to 110 in mushrooms, and 112 in plants, always by N-terminal elongation[8] (Fig. 1). The number of invariable positions in 29 species ranging from man to wheat is 35, *i.e.* approximately one third of the residues. Statistical calculations indicate that the number of invariant residues will not fall below 32[8]. An invariable sequence of 11 residues is found (positions 70 to 80 in the numbering of mammalian cytochromes c). The invariant residues contribute on the one hand to the

formation of a central hydrophobic pocket and to the bonding with the heme, which is enclosed in this pocket, and on the other to bonding with enzymes such as cytochrome oxidase.

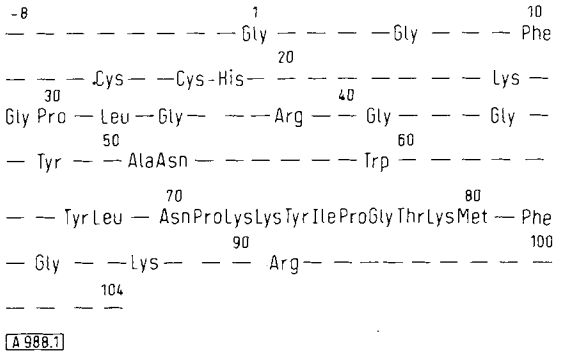


Fig. 1. Structural pattern of the cytochromes c. Residues indicated are constant in the cytochromes c presently known (after [9]).

Buried invariant residues: The heme is bonded to the peptide chain by two sulfide linkages connecting cystine residues 14 and 17. The heme iron, on the other hand, is hexacoordinated with the four nitrogens of the porphyrin, one nitrogen of the imidazole ring of histidine 18, and the sulfur of methionine 80. The heme is also tightly enclosed in a hydrophobic pocket (Fig. 2). The long invariable sequence 70—80 is folded in such a way as to form one wall of the apolar pocket, and the hydrophobic residues in the immediate vicinity of the heme on either side have the greatest tendency to remain invariable or to undergo conservative hydrophobic substitutions. Of the 26 hydrophobic residues (Val, Leu, Ile, Met, Phe, Pro) found in horse cytochrome c, nine are invariant, ten undergo conservative substitutions, and six are replaced by nonhydrophobic residues (Table 1). The pocket never contains charged residues.

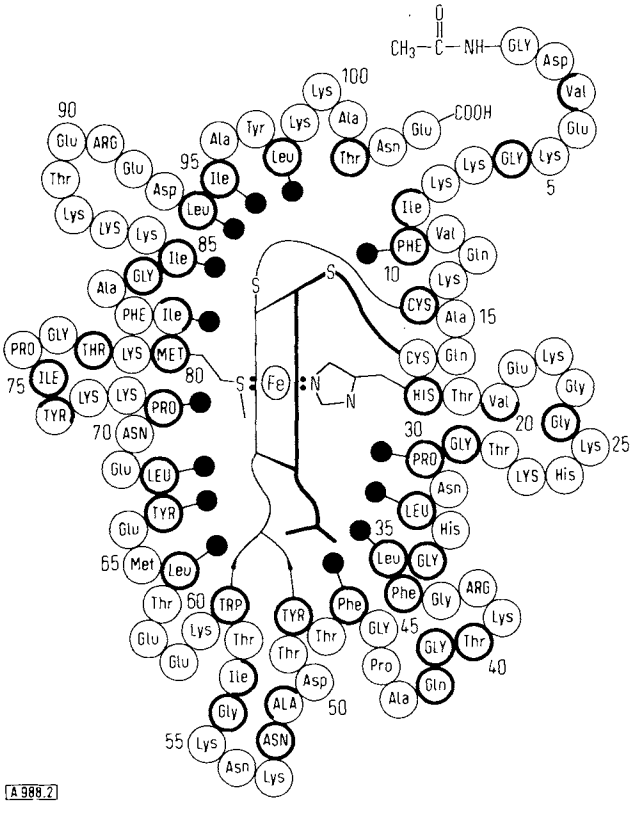


Fig. 2. Heme packing diagram of the cytochrome c molecule (schematic). *Heavy circles* indicate residues that are buried in the interior of the molecule, and attached *black dots* mark side chains which pack against the heme. *Light circles* indicate residues on the outside of the molecule, and *dark half-circles* show groups that are half-buried at the surface. *Arrows* from tryptophan 59 and tyrosine 48 to the buried propionic acid group represent hydrogen bonds. Residues designated by *capital letters* are totally invariant among the proteins of 29 species (after [8]).

Table 1. Variability of amino acid residues in cytochromes c (comparison of horse cytochrome c with those of 28 other species).

Residue type	Total number of residues	Invariant	With a conservative substitution [a]	With a radical substitution
Acidic (Asp, Glu)	12	0	1	11 (92%)
Basic (Lys, Arg)	21	7	1	13 (62%)
Ambivalent (Asn, Gln, Ser, Thr, His, Tyr, Trp, Cys, Ala)	34	11	13	10 (30%)
Hydrophobic (Val, Leu, Ile, Met, Phe, Pro)	25	9	10	6 (24%)
Glycine	12	8	3	1 (8%)
Total	104	35	28	41

[a] Conservative substitutions involve changes within the classes shown at left; in addition, exchange of Ala with residues of the hydrophobic class and of Gly with those of the ambivalent class are also regarded as conservative (after [8]).

Surface invariant residues: The polar residues on the surface of the globular proteins either play a part in the interactions (active sites), or ensure the correct folding of the chain by remaining in the aqueous medium, or, in the case of charged residues, ensure a suitable equilibrium of the basic and acidic groups to maintain an optimum pH for the molecule. Table 1 shows that the basic residues (lysine and arginine) are fairly often invariant, unlike the acidic residues. It is known that the cytochrome c-cytochrome oxidase interaction requires the participation of one or more lysine residues of the cytochrome c, particularly lysine 13 in horse cytochrome, since blockage by acetylation or succinylation inhibits the association.

X-ray studies show that the acidic and basic residues are separated on the surface of the molecule, with two basic zones surrounding an acidic zone, and that the substitutions lead to little change in this general arrangement. This distribution, which is unusual in globular proteins, undoubtedly allows recognition of, and association with, other macromolecules (reductase, oxidase, mitochondrial membrane). The lysine 13 that is involved in the association with cytochrome oxidase is situated just above the pocket in which the heme is accommodated. This position is occupied either by a lysine residue or by an arginine residue (conservative substitution) in the various cytochromes c.

Invariability of glycines and prolines: Out of 12 glycine residues found in horse cytochrome c, eight are invariable and three undergo conservative substitutions (Table 1). These residues, which present no steric hindrance, are situated in positions where only these residues can be inserted to ensure the preservation of the general conformation, particularly at the corners and close contacts of the chains. Of the four prolines, three are invariable and are situated at angles.

2.1.1.2. The Globins

It is possible to distinguish three families, *i.e.* the myoglobins, the α-hemoglobins, and the β-hemoglobins, which are three variations on a common theme.

Myoglobin: Myoglobin is an oxygen-storing protein found in the muscles of vertebrates. The group of fully sequenced myoglobins is limited at present to about a dozen mammalian species; the N-terminal sequences of the myoglobins of chicken and of coelacanth are also known. However, it is interesting to consider the myoglobins after the cytochromes c, since on the one hand the three-dimensional structure of sperm-whale myoglobin is known[10, 12a], and on the other this is again found to be a single peptide chain combined with heme. Of 153 residues contained in the chain, 99 are invariant[11, 12]. It is difficult to establish how many of these are truly invariant, since practically no myoglobins of lower vertebrates are known. The heme, which is attached to the chain only by secondary bonds, is connected *via* the hexacoordinated iron to a nitrogen of the imidazole ring of histidine 93 and to molecular oxygen. Moreover, the heme is embedded in a pocket edged with hydrophobic residues.

The chain has eight helicoidal segments and forms roughly a compact globule with the hydrophobic groups inside and nearly all the polar and charged groups on the outside. Human myoglobin and sperm-whale myoglobin differ in 26 residues. If the three-dimensional structure of sperm-whale myoglobin is taken as the model, it is found that 20 substitutions have taken place in surface positions of the molecule, two on the surface of pockets, and four in the interior of the protein. Three differences in the interior result from hydrophobic substitutions (no. 28: Ile-Val; no. 99: Val-Ile; no. 142; Met-Ile). The fourth (no. 110: Ala-Cys), which had already been observed in the interior of α-hemoglobin, could concern an unreactive residue[11]. The invariability of the hydrophobic interior is thus remarkable.

Myoglobin apparently has no precise surface constraints (interactions with other proteins *etc.*), and the surface residues should theoretically be easily varied. However, this does not seem to be the case.

Human myoglobin has three times as many residues in common with the myoglobins of other mammals as with the α and β chains of human hemoglobin, and it is clear that the myoglobins form a distinct family. It is nevertheless remarkable that the general conformation of myoglobin is found not only in the chains of vertebrate hemoglobins but also in the monomeric hemoglobins of certain invertebrates.

α and β Hemoglobins[17]: The normal hemoglobin of all vertebrates, with the exception of the cyclostomes, consists of four polypeptide subunits, two of an α type and two of a β type, forming a roughly spherical globule with a diameter of 50 to 60 Å. Two or three hemoglobins differing from one another in the sequence either of the α chain or of the β chain are sometimes found in a single species, and it is difficult to tell *e.g.* which of the two or three α chains belongs to the normal line. Nevertheless, it may be considered that there are at least two quite distinct families, that of the α hemoglobin and that of the β hemoglobin, which must have separated after the appearance of the cyclostomes and before the appearance of fishes. The invariability of the residues is determined here not only by the need for a hydrophobic internal part and the polypeptide-heme contacts, as in the case of myoglobin, but also by the contacts between the α and the β chains that are necessary to the preservation of the tetrameric structure of hemoglobin.

The two families of proteins include a relatively large number of known molecules from mammals[6, 13], as well as the α chains of a species of birds[14] and of a species of fish[15] and the β chain of an amphibian species[16]. The three-dimensional structure of horse hemoglobin was determined by *Perutz et al.*[18], who have established the details of the tetrameric architecture of the molecule. It was confirmed that the α and β chains have a secondary structure resembling that of myoglobin, though the amino-acid compositions are rather different. Each is found to have the seven or eight helicoidal segments and the heme insertion pocket. *Perutz* succeeded in localizing the residues that are bonded to the heme on the one hand and those that are in contact in the α_1-β_1 and α_1-β_2 interactions on the other. In the α chain (141 residues), eighteen residues are in contact with the porphyrin nucleus of the heme and the histidine residue 87 is coordinated to the iron. Sixteen residues are involved in the α_1-β_1 contacts and ten in the α_1-β_2 contacts (Fig. 3). In the β chains (146 residues), 20 residues are in contact with the porphyrin nucleus of the heme and the histidine residue 92 is coordinated to the iron. Eighteen residues are involved in the β_1-α_1 contacts and nine in the β_1-α_2 contacts. The contacts between peptide chains and heme or between peptide chains of different types are mainly apolar, whereas the contacts between identical chains are few in number and polar.

The mutations of human hemoglobin have been investigated by *Perutz* and *Lehmann*[19], who found that those affecting the residues in contact with the heme or involved in the α-β contacts are nearly always pathological, while those affecting superficial residues, which are generally polar, usually have no clinical significance. This observation should be correlated with the fact that the residues in contact with the heme or involved in α-β interactions are generally invariant (at least in mammals). In the family of β chains, for example, there are 70 invariant residues out of 146 in mammals, but

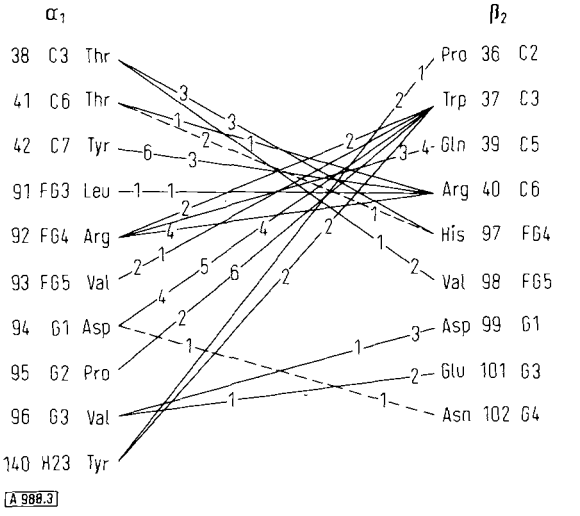


Fig. 3. "Vital" contacts between residues of unlike chains (α_1-β_2) in hemoglobin. The contacts comprise 10 residues in α_1 and 9 residues in β_2, all being invariant except residues no. 38 and 96 in α_1 and no. 39 and 101 in β_2. Plain connecting lines indicate van der Waals contacts; broken ones indicate that the contact includes a hydrogen bond. The numbers on the lines give the number of atoms contributed to the contact by the two residues on each side (after [18]).

this number falls to 54 when the β chain of the frog *Rana esculenta* is included in the family[16]. Out of the 21 residues in contact with the heme, 16 are invariant (76%). Of the nine residues involved in the "vital" α_1-β_2 contacts (Fig. 3), seven are invariant (87%), whereas of the 17 residues involved in the α_1-β_1 interactions, only eight are invariant (45%) in all the β chains known at present. Of the 100 residues without contact, 25 are invariant. Two long sequences (residues 30—40 and 96—108) are almost entirely invariant, and this rather exceptional character can be explained by the succession of residues that take part in the essential contacts.

2.1.1.3. Pancreatic Serine Proteases

Both the sequences[20-23] and the three-dimensional structures[24-26] are known for four proteolytic enzymes of the pancreas, *i.e.* chymotrypsins A and B, trypsin, and elastase. Though they belong to phylogenetically different families, the homology of their sequences and the characters of their active centers suggest that the respective structural genes are derived from a common ancestral gene[27]. It is interesting to note that the positions occupied by identical residues are usually those situated in the hydrophobic interior[26].

All the chemical and crystallographic data thus clearly indicate that in globular proteins the residues involved in the construction of the central nucleus, in the constitution of pockets containing a prosthetic group of hematinic nature, or in the interactions between subunits are usually hydrophobic and invariant in the course of evolution, whereas the residues situated on the surface are hydrophilic and lend themselves fairly readily to substitutions. It can be deduced that changes that affected the central part had a profound effect on the general conformation and resulted either in the disappearance of the function and elimination of the protein or in the appearance of a very different function as a result of a new conformation and the creation of a new family of proteins. The filiation will then be difficult to detect both chemically and biologically.

2.1.2. The Sequential Variability of Proteins

The crystallography and the comparative chemistry of proteins show that the interior of the protein globule is resistant to evolutionary variation, whereas the surface part lends itself to amino-acid substitutions with a rhythm that varies with the protein. The biological importance of the surface of the molecule varies from region to region; the active sites of enzymes (site of catalysis, of specificity, of coenzyme attachment, *etc.*), the zones of interaction between subunits in polymeric enzymes, the sites for the attachment of protein hormones to their receptors, *etc.* are undoubtedly less variable than other parts whose function is limited to the presence of hydrophilic groups that indirectly ensure correct folding of the chain.

The few enzymes whose three-dimensional structures are known and for which the role of the surface can be studied have unfortunately not been examined comparatively in several species. The zones of contact of cytochrome c with cytochrome reductase or cytochrome oxidase are unknown; myoglobin and hemoglobin do not appear *a priori* to have a biologically functional surface. On the other hand, the comparison of proteolytic enzymes is interesting from this point of view.

2.1.2.1. The Biological Significance of Substitutions

If molecular evolution is assumed to be progressive, as morphological evolution is assumed to be, the substitutions in the functional sites are fundamental. One is led, in fact, to distinguish "neutral" substitutions, which do not affect function and which are probably the more numerous and may in some measure reflect the antiquity of the separation of two species, from "active" substitutions that modify the biological properties.

On the chemical level it is necessary to differentiate between conservative substitutions (replacement of one basic residue by another or of one hydrophobic residue by another) and alterative substitutions, though it is sometimes difficult to place the substitution in one category or in the other. Substitutions of chemically equivalent amino acids, such as Arg/Lys, Val/Ile, and Ser/Thr, seem more frequent if one examines a large number of sequences[6]. The problem is whether these should really be regarded as substitutions on the functional level. Nevertheless, on the genetic level they correspond to different triplets[2], and conservative replacement requires mutation as well as alterative replacement. The nature of the substitutions will thus depend on the genetic code (neighboring triplets) and on the physicochemical properties of the residues (neighboring functional groups and configurations). The second factor becomes increasingly important with increasing specificity of the function of the residue, and in the limiting case the residue is irreplaceable.

If we consider the "mutability" of an amino acid over a large number of proteins, regardless of the position occupied, we find for example that some, such as serine, are very readily substituted, whereas others, such as cysteine and tryptophan, show little tendency to undergo substitution[6]. The ease of substitution may depend on whether analogs exist among the 20 amino acids that occur in proteins. It would undoubtedly be necessary to inquire into the evolutionary factors that have limited the number of amino acids that occur in proteins to 20, which include a number of pairs that are practically identical.

2.1.2.2. Inequality of Substitution Rhythms in Protein Families

It is known that morphological evolution has no uniform rhythm, and that a given line can show periods of intense variations and other periods of very slight mutability or even almost total arrest, as in the case of living fossils. Since each organism contains an extremely varied protein population, one might ask whether all the families of proteins vary with a more or less similar rhythm or whether each family has its own particular fate. In fact, the various organs evolved with different rhythms, undoubtedly depending on function, and the same must be true of the proteins.

If it is assumed *a priori* that the structural genes have the same variability, the difference in the substitution rates should depend on the percentage of residues that perform a function. This hypothesis cannot yet be verified, but the number of point mutations undergone in each family can be estimated by considering the substitutions, the genetic code, and the superposition of substitutions, referring this number to 100 residues, and expressing it per 100 million years (Table 2)[6]

Though the values are very approximate, and are particularly open to criticism on the ground that they presuppose a uniform

Table 2. Number n of accepted point mutations per 100 residues and per 100 million years [a].

Proteins	n
Fibrinopeptides	90
Growth hormone	37
Pancreatic ribonuclease	33
Immunoglobulins	32
κ chain, C region	39
κ chain, V regions	33
γ chain, C regions	31
λ chain, C region	27
Lactalbumin	25
Hemoglobin chains	14
Myoglobin	13
Pancreatic secretory trypsin inhibitor	11
Animal lysozyme	10
Gastrin	8
Melanotropin β	7
Myelin membrane encephalitogenic protein	7
Trypsinogen	5
Insulin	4
Cytochrome c	3
Glyceraldehyde 3-phosphate dehydrogenase	2
Histone IV	0.06

[a] For most of the proteins the time was extrapolated from probable time of divergence of the mammalian orders at 75 million years ago. For lysozyme, trypsinogen, insulin, glyceraldehyde 3-phosphate dehydrogenase, and histone IV the following times for the divergence of other lines from the mammalian line were used: birds, 300; fish, 400; insects, 900; and plants, 1500 million years (after [6]).

rate of variation within a given line of proteins, it is clear that some families vary much more than others.

It is difficult to understand why the family of myoglobins is more stable than that of the α and β chains of hemoglobin, whereas the functional constraints are apparently smaller in the former case, and also why the β family is more variable than the α family though the two chains appear to have exactly the same role. Cytochrome c is particularly stable, but the bewildering immutability of the histones (those of peas and beef differ in only two residues though the divergence of the lines occurred 1500 million years ago) remains a mystery.

2.1.2.3. Phylogeny and Drift of the Proteins

Paleontology shows us approximately when the lines of vertebrates diverged, and it is possible to compare the divergence times on the one hand and the numbers of substitutions observed on the other for several families of proteins. It appears that the number of substitutions increases with increasing time since divergence. With the aid of certain assumptions it is possible, by calculation, to construct phylogenetic trees based only on the number of substitutions[6, 28], and these trees correspond fairly closely to those derived from paleontological data.

The fact that in a given family of proteins, *e.g.* the β-hemoglobins (Table 3), the number of substitutions between two species is a function of the divergence time and is independent of the species chosen strongly suggests that the substitutions observed are mostly neutral from the standpoint of natural selection. The sequences of proteins would thus be biological "clocks". Since the zoological groups are defined by the morphologies, which become increasingly different with increasing time since the separation of the lines, the percentage of substitutions with respect to a reference species should in principle allow the identification of the class or subclass of the species from which the protein was obtained. However, it is necessary to choose a recent reference species; the lamprey, for example, belongs to a line that branched off from that leading to the other vertebrates about 500 million years ago, and the percentage of substitutions with respect to the proteins of this species should theoretically be of the same order for nearly all vertebrates.

Table 3. Percentage n of substitutions in the amino-acid sequence of β-hemoglobins of various species and paleontological time of divergence since the common ancestor.

Zoological classification	t [10^6 a]	n [%]
Class Mammalia		
Subclass: Eutheria		
Order Primates		
Hominoidea		
(man)	0	0
(gorilla)	20	1
Cercopithecoidea		
(rhesus monkey)	60	5
Order Artiodactyla		
Ruminantia		
(sheep)	75	18
Suiformes		
(pig)	75	16
Tylopodes		
(llama)	75	14
Order Perissodactyla		
(horse)	75	17
Order Rodentia		
(mouse)	75	18
Subclass Metatheria		
Order Marsupialia		
(kangaroo)	130	26
Class Amphibia		
Order Anura		
(frog)	320	46

It should be noted that, while roughly equal percentages of substitutions are found for similar divergence times, this does not mean that the modified positions in the polypeptide chains are the same. On the other hand, there are exceptions, since the birds have the same neurohypophyseal hormones as the amphibians, from which they diverged about 350 million years ago, whereas they are different from the mammals, from which their divergence was more recent. Thus, while the drift of proteins, a passive phenomenon, is numerically large, it must not be allowed to mask the true evolution, which must by definition be accompanied by a change in function.

2.2. The Length of the Polypeptide Chain

On examining a line of homologous proteins, one cannot help noticing that the number of residues remains practically constant. All the cytochromes c of vertebrates contain 104 amino-acid residues, all the α-hemoglobins have 141—142 residues, all the neurohypophyseal hormones have 9 residues, *etc.* To explain this stability it is necessary to consider the mechanism of protein biosynthesis; this involves transcription of the structural gene, which is a deoxyribonucleic acid (DNA), into a messenger ribonucleic acid (mRNA), followed by translation of the mRNA into an amino-acid sequence. One mRNA codes several proteins, and the translation of each involves the reading of a sequence of triplets from an initiating triplet (AUG or GUG) to a terminating triplet (UAA, UAG, or UGA). In addition to the RNA polymerase of the particular transfer RNAs, which recognize the initiation and termination signals, protein factors that have not yet been satisfactorily

identified also take part in this process[29]. It is strange to find that a phenomenon that involves such a large number of molecules, and which is therefore very susceptible to the action of mutations, can lead to a practically constant result. The few variations observed are therefore particularly instructive.

2.1.1. Shortening and Elongation of the Chain

The known families of homologous proteins include few representatives from lower species. In some cases observed (cytochromes c), a slight shortening appears to have occurred in higher vertebrates.

2.1.1.1. N-Terminal Modification of the Chain

The cytochromes c of plants, mushrooms, and insects respectively contain 8, 6—4, and 4 residues more than those of vertebrates, these extra residues forming an N-terminal elongation of the chain[9]. It appears that the initiation signal has been displaced and that a later initiation gives a shorter chain in the higher species.

However, this is not a general phenomenon, since the hemoglobins of invertebrates and the corresponding proteins of plants have roughly the same number of residues as the α or β chains of vertebrate hemoglobins. An N-terminal deletion of six residues is observed in frog β-hemoglobin[16], but the shortening does not seem to have any evolutionary value; nevertheless, it appears that the N-terminal ends of the chains are more susceptible to variation than the central part.

2.2.1.2. C-Terminal Modification of the Chain

Shortening or elongation seems to be less frequent at the C-terminal than at the N-terminal end, as if the termination signal were less susceptible to displacement or as if displacement were incompatible with the preservation of a functional molecule.

The presence in pigs and other mammals of a peptide known as α-melanocyte stimulating hormone (α-MSH) because of its special biological properties and having the sequence of the first 13 residues of corticotropin, which itself has 39 residues, could point to a premature termination of corticotropin biosynthesis. In a recently isolated abnormal human hemoglobin known as Constant Spring (CS) hemoglobin, the α chain contains 172 residues instead of the usual 141. It is interesting to note that this is due to an elongation of 31 residues at the C-terminal end, as if the termination signal had been displaced in the direction of an elongation[30]. A C-terminal elongation of 10 residues has also been observed in a β chain of a human hemoglobin[31]. Though CS hemoglobin represents only 1—2% of the total hemoglobin in the case studied, and the molecules in question are abnormal, it is conceivable that the mechanism shown here could occur in the course of evolution.

2.2.2. Insertion and Deletion in the Interior of the Chain

On comparison of homologous proteins, one sometimes finds that a given species has one or two additional residues or the absence of one or two residues in relation to the general molecular pattern. For example, carp α-hemoglobin has 142 residues instead of 141 (insertion), and the β-hemoglobins of cattle and of sheep have 145 residues instead of 146 (deletion). The homology of the sequences allows the localization of the variation in the interior of the chain. Insertions and deletions of this nature have been observed in abnormal human hemoglobins, and it is possible to explain these observations by an intragenic crossing-over that affects the peptide sequences. The central insertions and deletions appear to affect at most five consecutive residues, and often fewer. Their influence on the general conformation and function generally seems to be slight.

3. Polymorphism : Isoproteins

The extreme purification of proteins has shown that the same tissue of the same species quite often contains two or more molecules that apparently perform the same function and have very similar amino-acid sequences. This polymorphism is not due to incomplete dominance, since each protein corresponds to a different structural gene. These molecules have been named isoproteins (isoenzymes, isohormones), and have been assumed to result from duplication of an initial structural gene. It should be noted that while some proteins are more likely to exhibit polymorphism than others and the degree of polymorphism depends on the species, it is very unusual for a protein not to exhibit this phenomenon. Thus, cytochrome c, which does not appear to show the phenomenon in vertebrates, occurs in yeast in the two forms iso-1-cytochrome c and iso-2-cytochrome c[32].

The biological significance of this multiplication is not clear. It is possible that the existence of two or more genes that produce proteins having similar functions protects the species against an inactivating mutation, which would be lethal in the case of a single gene. It is also conceivable that successive mutations ultimately bring one of the proteins to the point where it can perform a different function, and that this is the first step in the formation of a new protein. It may nevertheless be noted that the proportions of the isoproteins vary considerably, and that the disappearance of the most abundant isoprotein by mutation does not seem to be accompanied by a corresponding rise in the quantities of the less abundant ones.

The definition of the isoproteins is not very specific, but since proteins are usually named according to their function they are generally proteins having almost identical biological activities but relatively different amino-acid sequences.

3.1. Strict Isoproteins: The Chymotrypsinogens

The chymotripsinogens A and B have been found in beef pancreas. They are similar in size, both consisting of a polypeptide chain of 245 residues, and very probably also in conformation[21]. The activations of these chymotrypsinogens by trypsin, which involve the scission of an Arg 15-Ile 16 linkage, are similar, though chymotrypsinogen B is activated 15 times as quickly under comparable conditions. Since the only substitution in the first 35 residues of the chain is an alanine in the B protein in place of a serine in the A protein, it appears that the activation region in the former could be more flexible because of the absence of a hydrogen bond. Two of the three autocatalytic cleavages that follow activation in chymotrypsinogen A are also found in the activation of the B protein, and the specificities of the enzymes are practically identical.

It is remarkable that the two chymotrypsinogens, which are functionally so nearly identical, differ in 52 residues, *i.e.* in 21% of the sequence, and are produced in roughly equal quantities by the pancreas. At first sight there seems to be no reason for the duplication. In fact, it must have happened twice, since a less well-characterized chymotrypsinogen C has also been isolated. The three enzymes also occur in pigs, but the study of other species has not progressed sufficiently to show whether this is a general phenomenon among the vertebrates.

3.2. Derived Isoproteins: The Globins

The hemoglobins of vertebrates, with the exception of the cyclostomes, are tetrameric molecules containing two types of chains α and β such that they can be characterized by the formula $\alpha_2\beta_2$. The α and β chains are isoproteins in the sense that their functions are apparently similar, whereas their sequences, though related, are different. The complete sequences of these chains are known for some 20 species of vertebrates, mostly mammals, and the duplication may be assumed to be a general phenomenon. Moreover, polymorphism occurs even in species having monomeric hemoglobins, such as the lamprey and the invertebrates, and the corresponding proteins of plants.

The α and β chains are roughly equal in length (141 residues for the α chain and 146 for the β chain) and their conformations, which are very similar[18], closely resemble that of myoglobin. In man there is 57% substitution between the α and the β chains. A minor hemoglobin having the formula $\alpha_2\delta_2$ is also found, the δ chain, like the β chain, containing 146 residues and differing from the latter in only 7% substitution[6]. The fetus also contains a special hemoglobin having the formula $\alpha_2\gamma_2$, in which the γ chain has 146 residues like the β chain, and differs from the latter in 27% substitution. Other chains, ε and ζ, exist in the embryo, but these have not yet been characterized. In other species of mammals it is not unusual to find two or more hemoglobins in the adult that differ from one another either in the α or in the β chain, so that while there is always at least one representative of the α type and one of the β type in a given species, several proteins of each type, each corresponding to a different structural gene, may exist in variable proportions.

It is therefore possible to distinguish here two degrees of polymorphism and two categories of isoproteins, *i.e.* the strict isoproteins having the same number of residues (*e.g.* the group β, δ, and γ) and the derived isoproteins, which do not have the same number of residues and which also exhibit a higher degree of substitution between them. If it is accepted that the percentage of substitution reflects the time that has elapsed since the duplication, *i.e.* the evolutionary distance, one can assume, taking man as an example, that the α-β duplication with 57% substitution was the earliest, the β-γ duplication with 27% substitution was later, and the β-δ duplication with 7% substitution was the most recent.

Moreover, since the myoglobin in the muscle performs a function very similar to that of hemoglobin, and the chain length (153 residues) and particularly the conformation are similar to those of the α and β chains[18], it may be regarded as a derived isoprotein. Human myoglobin differs from the human α chain in 74% substitution[33], and the duplication would thus have been earlier than the α-β duplication. It is interesting to note that the difference in length arises only when the substitution is greater than 50%, *i.e.*, in the interpretation adopted, when the duplication is already very old. If the first duplication of the globins is assumed to have been the myoglobin-α chain duplication[3], it must be observed that the protein that became myoglobin does not appear to have duplicated further and has undergone fewer substitutions than the proteins that became the chains of hemoglobin. The factors that lead one structural gene to undergo duplication more readily than another are as obscure as those that favor substitutions in one line rather than in another.

4. The Biological Differentiation of Proteins

4.1. Differentiation by Substitutions: Analogous Proteins

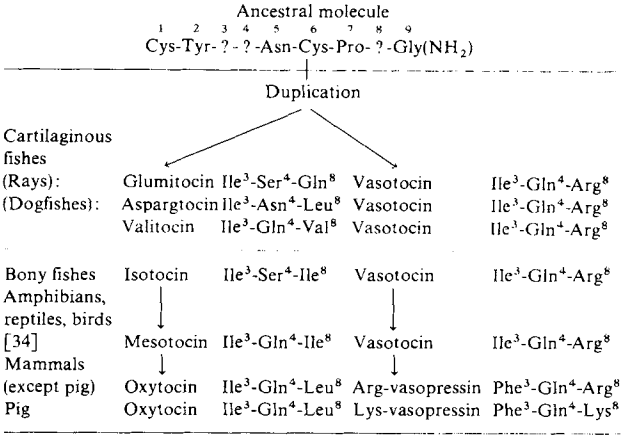
Certain proteins that have different biological properties are found to be so similar in the numbers of residues and in the amino-acid sequences that it is plausible to regard them as being derived from a common molecular stock. These functionally different but chemically related proteins may be referred to as analogous proteins. The degree of resemblance obviously varies within each group, and the relationship may be disputable in the limiting case.

4.1.1. The Neurohypophyseal Hormones

Although these are peptides and not proteins, the example may serve to illustrate the transformation of isologous proteins into analogous ones. Nine neurohypophyseal hormones, all of them nonapeptides, have now been identified in some 40 species belonging to all classes of vertebrates except the cyclostomes (Table 4, Fig. 4).

The biological activities of the peptides of lower vertebrates have been measured mainly in mammals, so that their true function is not well known. Nevertheless, it is interesting to note that in the classes that preceded the mammals, such as the amphibians and the reptiles, mesotocin (Ile^8-oxytocin) and arginine vasotocin (Arg^8-oxytocin) both possess a pronounced oxytocic activity and that they could be considered as isopeptides. However, the vasotocin also takes part in the regulation of water and electrolytes, and is thus capable

Table 4. Hypothetical scheme of the evolution of neurohypophyseal hormones. One gene duplication and a series of subsequent single substitutions in positions 3, 4, or 8 produce two molecular lines.



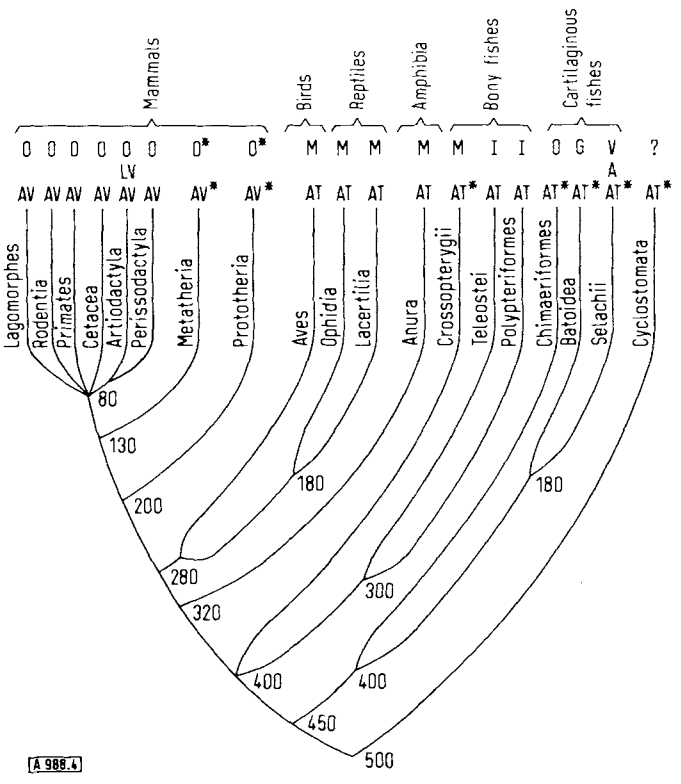


Fig. 4. Neurohypophyseal hormones and species evolution according to paleontological data. Letters indicate hormones identified in modern representatives of the groups (an asterisk means that identification is not chemical but pharmacological). O, oxytocin; AV, arginine vasopressin; LV, lysine vasopressin; M, mesotocin; I, isotocin; A, aspargtocin; V, valitocin; G, glumitocin; AT, arginine vasotocin. The numbers give the time in millions of years since the divergence. (The formulas of the hormones are given in Table 4.)

of acting on receptors on which mesotocin has no action. Two new molecules, oxytocin and usually arginine vasopressin (Phe^3-Arg^8-oxytocin), act on different receptors in mammals, the former acting on the uterus and the mammary gland and the latter on the kidney. The reciprocal activities are negligible, and the similarity was established only after the determination of the chemical structures.

It may be assumed that the functional differentiation of proteins, though more complicated than that of peptides, could have occurred progressively after the duplication by substitutions and by modification of the chain length, but that at a certain degree of differentiation the functions become quite separate though the structures are still related.

4.1.2. The Pancreatic Serine Proteases

Three proteolytic enzymes of the pancreas, *i.e.* chymotrypsin, trypsin, and elastase, while having different specificities, have been found to be analogous, first by determination of the amino-acid sequences[20-23] and then by comparison of the conformations[24-26]. The chain lengths are slightly different: 241 residues for beef chymotrypsin A, 223 residues for beef trypsin, and 240 for pig elastase. The general conformations are remarkably similar, but the differences in specificity can be explained by specific variations in the conformation of the substrate binding site[34a].

Trypsin, chymotrypsin, and elastase all have a pocket, which engages the side chain of the amino-acid that determines the specificity (Fig. 5). If the numbering of beef chymotrypsinogen A is used for these three enzymes, the position 216 bordering the mouth of the pocket is occupied by a glycine residue in trypsin and in chymotrypsin, which allows the introduction of a long, bulky side chain, and by a valine residue in elastase, which restricts access to small aliphatic residues. At the base of the pocket, on the other hand, position 189 is occupied by aspartic acid in trypsin, which allows ionic bonding with basic residues, while this position in chymotrypsin is occupied by serine, which cleaves peptide linkages at neutral hydrophobic residues[26]. The differentiation of the specificities here appears to be based on alterative substitutions. The data on the "trypsin-like" and "chymotrypsin-like" enzymes of lower vertebrates may allow the evolutionary history of the substrate pocket to be traced. A common feature that has been retained by the pancreatic serine proteases is the hydrolytic action mechanism, and the functional differentiation is apparently limited to the specificity of substrate binding.

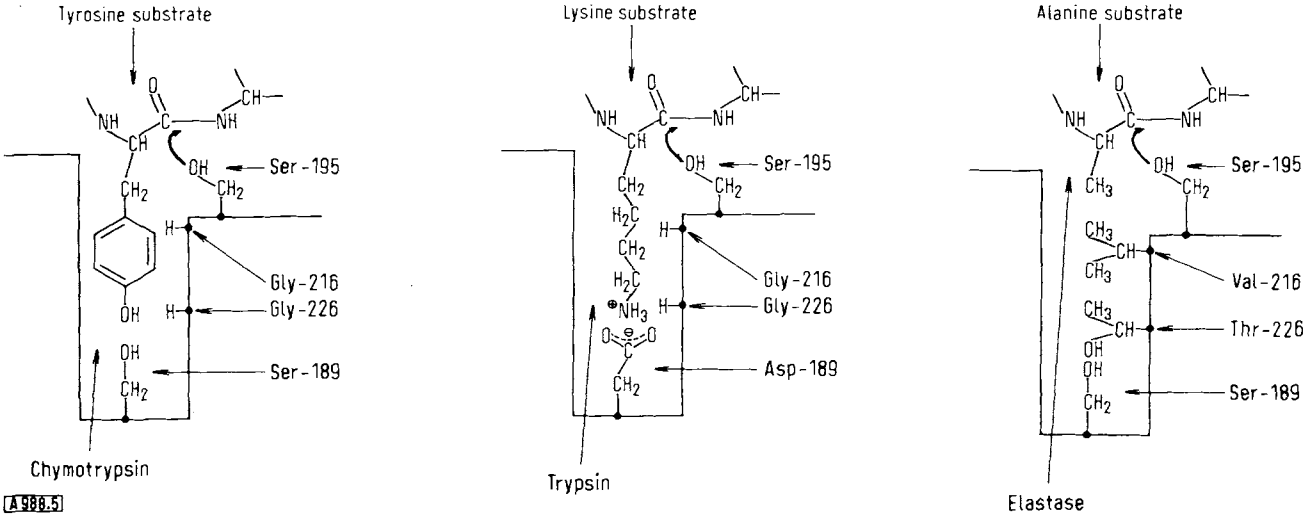


Fig. 5. Differences between the substrate binding sites of chymotrypsin, trypsin, and elastase (schematic). The nucleophilic attack of the active center serine γ-oxygen upon the substrate is indicated by the curly arrow (after [34a]).

4.2. Differentiation by Hybridization

When two similar structural genes (*e.g.* coding two isoproteins) are situated on the same chromosome, faulty alignment of

the chromatids during the synapsis is possible, with crossing-over of the non-allelic genes. After separation, the two chromosomes each possess a hybrid gene, but one of the hybrids has the initial part of the first parent gene joined to the terminal part of the second, while in the second hybrid the situation is reversed. Consequently, one of the hybrid genes

The ferredoxin found in bacteria consists of a chain of 55 residues having an internal symmetry, with 44% homology between the two halves of the chain in the ferredoxin of *Clostridium pasteurianum* (Fig. 6). This symmetry has also been found in other bacteria, and points to an intragenic duplication.

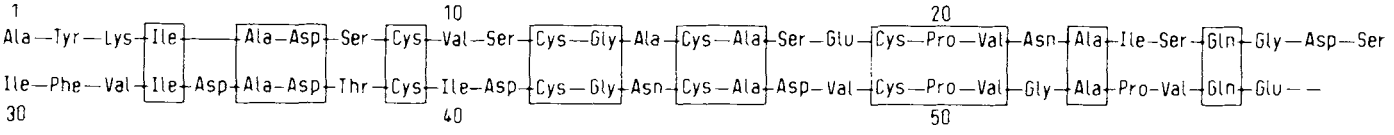


Fig. 6. Homologies between the two halves of the ferredoxin molecule of *Clostridium pasteurianum* suggesting an intragenic duplication (after [6]).

will code a polypeptide chain having the N-terminal sequence of one protein and the C-terminal sequence of another.

Hybridization between the β and δ chains of hemoglobins is a typical example. Lepore human hemoglobin, which is a hemoglobin resulting from a mutation, consists of a normal α chain and a hybrid δ-β chain. Anti-Lepore hemoglobin consists of a normal α chain and a hybrid β-δ chain. The β and δ chains both contain 146 residues, as do the two hybrids β-δ and δ-β. In Boston Lepore hemoglobin residues 1—87 correspond to the δ chain and residues 116—146 to the β chain. Since the δ and β chains have the same sequence for residues 88—115, the crossing-over site cannot be exactly localized.

In Miyada anti-Lepore hemoglobin, the β-δ chain has residues 1—12 of the β chain and residues 22—146 of the δ chain; since the sequence 13—21 is common to both chains, it has not been possible to localize precisely the crossing-over site.

Hybridization has also been postulated in the case of the clupeines from herring sperm[6]. Clupeine Z is identical with clupeine YI in the sequence 1—6 and with clupeine YII in the sequence 6—30.

Hybridization between genes may be limited to genes of identical length, *i.e.* formed by an earlier duplication, but it represents an accelerated differentiation mechanism in relation to differentiation by point mutations involving the substitution of amino acids one at a time.

4.3. Differentiation by Intragenic Duplication

Certain proteins appear to have repetitive regions along their polypeptide chain that suggest that after duplication of the ancestral structural gene the two daughter genes combined and continued to function as a single gene. The length of the chain was thus doubled. Though the mechanism of such intragenic duplication is not very well understood, this interpretation could account for the discontinuous elongation of the polypeptide chains and for a certain periodicity in the amino-acid sequences.

4.3.1. Ferredoxins

Ferredoxin is a non-heme protein containing iron, and is found in photosynthetic anaerobic bacteria, blue-green algae, green algae, and higher plants. It takes part in a wide variety of biochemical processes such as photosynthesis, the fixation of nitrogen, the reduction of sulfate, dehydrogenations, and redox reactions.

On the other hand, the ferredoxin found in higher plants such as spinach has a chain about twice as long (97 residues) as those of the bacterial ferredoxins, while that of *Chromatium sp.* is of intermediate length (81 residues). All these ferredoxins have a homologous region, the elongation with respect to the bacterial ferredoxins appearing to be at the N-terminal end in plants and at the C-terminal end in *Chromatium sp.* All the evidence suggests growth by intragenic duplication with a base unit corresponding to about 25—28 residues.

4.3.2. Immunoglobulins

Intragenic duplication also appears to have occurred in the immunoglobulins. It is known that the immunoglobulin molecule is built up symmetrically from two identical light chains (215—220 residues) and two identical heavy chains (446 residues), the four chains being joined by disulfide bridges. The fact that the length of the heavy chain is almost exactly double that of the light chain naturally suggests a duplication. On the other hand, there appears to be a symmetry in the light chain itself between the N-terminal half and the C-terminal half. The N-terminal half seems to be subject to substitutions and is described as variable (V), whereas the more stable C-terminal half is described as constant (C). The heavy chain appears to consist of one V unit and three C units, the elongation taking place discontinuously in blocks of 110 residues at a time.

5. Fusion of Proteins

The above examples illustrate how the evolution of proteins starting with an ancestral structural gene could have led, by duplications followed by point mutations and hybridization, to molecules having different sizes, sequences, and functions. However, new proteins could also be built up from proteins that are already well differentiated by fusion of polypeptide chains. This fusion may result from the fusion of adjacent structural genes, but also seems to occur without fusion of the genes, in which case each part of the sequence is still governed by an autonomous structural gene.

5.1. Bifunctional Enzymes by Fusion of Adjacent Genes

The biosynthesis of histidine in *Salmonella typhimurium* is controlled by an operon in which nine adjacent structural genes code the enzymes that take part in the synthesis of the amino acid. The second structural gene of the operon

codes the histidinol dehydrogenase and the third codes the imidazolylacetol phosphate:L-glutamate aminotransferase. The termination signal of the first enzyme and the initiation signal of the second are separated by a sequence of intercistronic nucleotides, which is not normally expressed. Following a double mutation, the punctuation signals have no longer been recognized, and a single gene formed by the sequence of the two original genes and the intercistronic region has been transcribed into a protein having a molecular weight of 140000, whereas the molecular weights of the dehydrogenase and of the aminotransferase are 59000 and 84000 respectively[35,36]. This fused protein has two catalytic activities and a dimeric structure like the original enzymes, which suggests that the conformations of the separate proteins have been preserved despite the covalent fusion. It may be assumed that the junction polypeptide region corresponding to the sequence of intercistronic nucleotides is particularly flexible.

It is possible that certain large enzymes such as β-galactosidase and DNA polymerase have resulted from fusions of this nature. Proteolytic cleavage of DNA polymerase could yield two fragments, each having one of the activities of the initial enzyme. The fusion of adjacent genes appears to be a plausible mechanism for the formation of complex proteins in the course of evolution.

5.2. Fusion of Proteins without Fusion of Genes

The immunoglobulins (see Section 4.3.2), which play an essential part in immunological reactions, are symmetrical molecules consisting of a pair of heavy chains and a pair of light chains. In man, immunoglobulins G (IgG), A (IgA), M (IgM), D (IgD), and E (IgE) have a heavy chain of the γ, α, μ, δ, and ε types respectively. These heavy chains are associated with light chains of two types, κ and λ. In mice 97% of the light chains are of the κ type, whereas in man one finds 66% of the κ type and 34% of the λ type[6,37]. The light chains (220 residues) consist of a variable (V) N-terminal half and a constant (C) C-terminal half. In the chains of the κ type examined so far, whereas the constant region (C_κ) behaves as if it were coded by a single gene, the V_κ region could correspond to three genes, in view of the three subclasses that can be distinguished. The amino-acid sequence of a given light chain would thus be controlled by two separate genes, one for each half. Similarly, in the heavy chains, the N-terminal quarter is described as the variable and the remainder as the constant region, and these two regions should be under the control of separate genes.

6. Polymeric Proteins and Immobilized Proteins

All the examples discussed above are concerned with the possible evolution of a single polypeptide chain, which is assumed to act independently in the performance of a function. However, it is clear from the number of units involved and the structure of the associations that cell physiology calls for more complicated protein systems.

The enzymes required for the essential regulation of metabolic chains[38] consist of subunits joined to one another by noncovalent bonds ("polymeric proteins"). These regulatory enzymes, which are often described as "allosteric", are generally sensitive to the action of the end product of a chain of enzymes which is *not* a steric analog of their substrate. A growing number of functions appear to depend on polymeric systems, examples being oxygen transport (hemoglobin) muscle contraction (myosin, actin), and hormone action (thyrotropin).

A general type of molecular assembly appears to be involved, the number of subunits that take part being variable but possibly very large. Except in the case of hemoglobin[118], little is yet known about the manner in which the subunits are associated. In any case, the adaptation of the conformations of the subunits to form a polymeric architecture presents an evolutionary problem if the associations are assumed to have been formed from free monomeric proteins (*e.g.* the α and β chains of hemoglobin). It is necessary here to envisage new constraints from the standpoint of natural selection, these constraints affecting the nature of the contact sites. The transition from a "monomeric" function to a "polymeric" function introduces a new element, that of structural coordination.

At a higher level of integration, the cell may be regarded as a microheterogeneous system in which the surface effects predominate over the statistical mass-action relations, and in the limiting case become responsible for the channeling of activities[39]. The proteins, and particularly the enzymes that are immobilized in the membrane structures, for example, then become dependent on the matrix in which they are incorporated as well as on their own biological function. Because of the multiplicity of the molecules involved (lipids, saccharides, *etc.*), the "microenvironment" should have a powerful effect on the conformation of the immobilized proteins. At this level of complexity it is difficult to perceive the point of impact of natural selection.

7. Conclusion

In order to establish a relationship between protein molecules it seems reasonable to compare cell differentiation and molecular differentiation. For example, the cells of both the anterior and intermediate lobes of the pituitary are derived from the buccal ectoderm; it is therefore very interesting that the α-MSH (13 residues) synthesized by the cells of the intermediate lobe represents the N-terminal part of the corticotropin synthesized by those of the anterior lobe. On the other hand, glucagon, a hyperglycemic hormone secreted by the α cells of the islets of Langerhans in the pancreas, and secretin, a hormone produced by the duodenal mucosa, which stimulates the secretion of pancreatic juice (29 and 27 residues respectively) have 15 amino acids in common, and also 7 conservative substitutions. The pancreas is differentiated from the duodenum, and this may explain the similarity. There is also a certain similarity between the extracellular proteins secreted by the glands derived from the endoderm[140]. Proteins as different as the proteolytic enzymes of the pancreas, the coagulation factors produced in the liver, and the pancreatic and gastric hormones have been grouped together under the heading of "enterosecretory proteins".

Though the evolution of proteins has occurred by specific chemical mechanisms, it is nevertheless only one aspect of the undissociable phenomenon of the evolution of organisms.

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[1] *F. Crick*, Nature 227, 561 (1970).

[2] *J. D. Watson*: Molecular Biology of the Gene. Benjamin, New York 1965.

[3] *V. M. Ingram:* The Hemoglobin in Genetics and Evolution. Columbia University Press, New York 1963.

[4] *A. S. Romer:* Vertebrates Palaeontology. University of Chicago Press, 1966.

[5] *R. Acher*, Angew. Chem. *78*, 856 (1966); Angew. Chem. internat. Edit. 5, 798 (1966).

[6] *M. O. Dayhoff:* Atlas of Protein Sequence and Structure. Vol. 5. National Biomedical Research Foundation, Washington 1972.

[7] *E. Mayr:* Principles of Systematic Zoology. McGraw-Hill, New York 1969.

[8] *R. E. Dickerson, T. Takano, D. Eisenberg, O. B. Kallai, L. Samson, A. Cooper*, and *E. Margoliash*, J. Biol. Chem. *246*, 1511 (1971).

[9] *E. L. Smith:* The Evolution of Proteins. The Harvey Lectures, Series 62. Academic Press, New York 1968, p. 231.

[10] *J. C. Kendrew*, Science *139*, 1259 (1963).

[11] *A. E. R. Herrera* and *H. Lehmann*, Nature New Biol. *232*, 149 (1971).

[12] *M. Dautrevaux* and *Y. Boulanger*, Bull. Soc. Chim. Biol. *49*, 949 (1967).

[12a] *R. E. Dickerson* in *H. Neurath:* The Proteins. 2nd Edit., Vol. II. Academic Press, New York 1964, pp. 603ff.

[13] *G. M. Air, E. O. P. Thompson, B. J. Richardson*, and *G. B. Sharman*, Nature *229*, 391 (1971).

[14] *G. Matsuda, H. Takei, K. C. Wu*, and *T. Shiozawa*, Int. J. Protein Res. *3*, 173 (1971).

[15] *K. Hilse* and *G. Braunitzer*, Hoppe-Seylers Z. Physiol. Chem. *349*, 433 (1968).

[16] *J. P. Chauvet* and *R. Acher*, Biochemistry *11*, 916 (1972); *G. Matsuda, T. Maita, K. Mizuno*, and *H. Ota*, Nature New. Biol. *244*, 244 (1973).

[17] Review: *G. Buse*, Angew. Chem. *83*, 735 (1971); Angew. Chem. internat. Edit. *10*, 663 (1971).

[18] *M. F. Perutz, H. Muirhead, J. M. Cox*, and *L. G. G. Goaman*, Nature *219*, 131 (1968).

[19] *M. F. Perutz* and *H. Lehmann*, Nature *219*, 902 (1968).

[20] *B. S. Hartley* and *D. L. Kauffman*, Biochem. J. *101*, 229 (1966).

[21] *L. B. Smillie, A. Furka, N. Nagabhushan, K. J. Stevenson*, and *C. O. Parkes*, Nature *218*, 343 (1968).

[22] *K. A. Walsh* and *H. Neurath*, Proc. Nat. Acad. Sci. USA *52*, 884 (1964).

[23] *D. M. Shotton* and *B. S. Hartley*, Nature *225*, 802 (1970).

[24] *D. M. Blow*, Biochem. J. *112*, 261 (1969).

[25] *R. M. Stroud, L. M. Kay*, and *R. E. Dickerson*, Cold Spring Harbor Symp. Quant. Biol. *36*, 29 (1971).

[26] *D. M. Shotton* and *H. C. Watson*, Nature *225*, 811 (1970).

[27] *H. Neurath* and *R. A. Bradshaw*, Accounts Chem. Res. *3*, 249 (1970).

[28] *W. M. Fitch* and *E. Margoliash*, Science *155*, 279 (1967).

[29] *V. M. Ingram* and *M. Grunberg-Manago:* Biosynthèse des Macromolécules. Ediscience, Paris 1970.

[30] *J. B. Clegg, D. J. Weatherall*, and *P. F. Milner*, Nature *234*, 337 (1971).

[31] *G. Flatz, J. L. Kinderlerer, J. V. Kilmartin*, and *H. Lehmann*, Lancet I, 732 (1971).

[32] *P. P. Slonimski, R. Acher, G. Pere,- A. Sels*, and *M. Somlo*, Colloq. Int. Cent. Nat. Rech. Sci. (1965).

[33] *A. E. R. Herrera* and *H. Lehmann*, Nature New Biol. *232*, 149 (1971).

[34] *R. Acher, J. Chauvet*, and *M. T. Chauvet*, Eur. J. Biochem. *29*, 12 (1972).

[34a] *D. Shotton* in *H. Fritz* and *H. Tschesche:* Proteinase Inhibitors. de Gruyter, Berlin 1971, pp. 47ff.

[35] *J. Yourno, T. Kohno*, and *J. R. Roth*, Nature *228*, 820 (1970).

[36] *M. M. Rechler* and *C. B. Bruni*, J. Biol. Chem. *246*, 1806 (1971).

[37] *H. M. Grey* in *E. Schoffeniels:* Biochemical Evolution and the Origin of Life. North-Holland Publishing Company, Amsterdam 1971, pp. 96–111.

[38] *G. Cohen:* Le métabolisme cellulaire et sa régulation. Hermann, Paris 1967.

[39] *E. Katchalski, I. Silman*, and *R. Goldman*, Advan. Enzymol. *34*, 445 (1971).

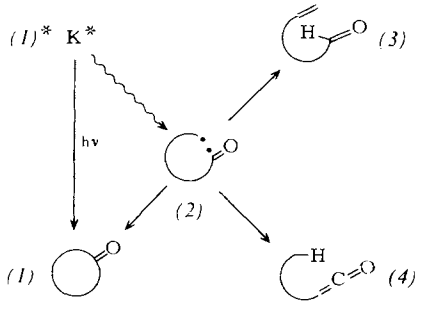
[40] *J. W. Adelson*, Nature *229*, 321 (1971).

COMMUNICATIONS

Stereospecificity as an Argument against the Intermediacy of 1,4-Alkyl/Acyl Diradicals in the Light-Induced Cyclobutanone-Tetrahydrofurylidene Isomerization in Condensed Phase[1]

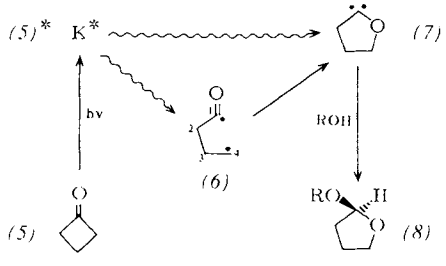
By *Gerhard Quinkert, Peter Jacobs*, and *Wolf-Dieter Stohrer*[*]

Four-membered cyclic ketones play a hitherto poorly understood role within the family of electronically excited cycloalkanones[2]. π*,n-Excited common-sized cycloalkanones ($m = 5$, 6, 7) *(1)** yield mainly isomeric enals *(3)*, ketenes *(4)*, and cycloalkanones *(1) via* 1,*m*-alkyl/acyl diradicals (α-oxo-α,ω-alkylenes) *(2)*[3] as primary photoproducts.



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π*,n-Excited cyclobutanones *(5)**, on the other hand, undergo stereospecific ring expansion[5] (with retention at C-4, which migrates from the C atom to the O atom of the carbonyl group) furnishing tetrahydro-2-furylidenes *(7)* which can be trapped by alcohols with the formation of acetals *(8)*[6].

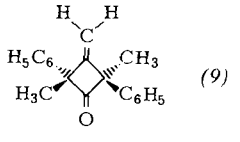


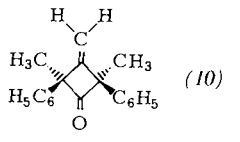
The stereochemical result corresponds with a reaction course which either excludes 1,4-alkyl/acyl diradicals *(6)* or permits these bifunctional intermediates only if they are configurationally stable at C-4. Since *Hoffmann*'s concept of through-bond coupling[7] attributes an enhanced rotational barrier to the 3,4-bond of 1,4 diradicals, the examples known until now[5] are unsuitable as a basis for unambiguously deciding between the above alternative modes of ring expansion by means of the criterion stereochemistry.

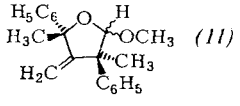
Configurationally isomeric 3-methylenecyclobutanone derivatives represent suitable test compounds: in the corresponding

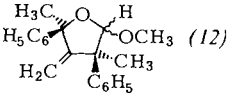
diradicals the configuration-preserving effect of through-bond interaction is overcompensated[8] by the configuration-changing effect caused by formation of the allyl system.

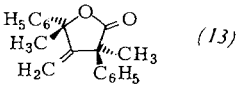
The stereoisomers *(9)* and *(10)* were prepared by conventional methods and their configuration established non-empirically by NMR spectroscopy of suitable derivatives[9]. UV irradiation of their methanolic solutions at room temperature yields a binary mixture of acetals in both cases. Chromic acid oxidation of the heterocyclic photoproduct *(11)*, obtained from *(9)*, affords exclusively *(13)* and that of the acetalic photoproduct *(12)*, derived from *(10)*, yields exclusively *(14)*. The configuration of the two γ-lactones follows from the formation of *(13)* [together with *(15)*] from *(9)* and of *(14)* [in addition to *(16)*] from *(10)* on Baeyer-Villiger oxidation.

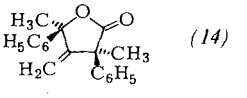

(9)

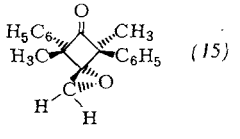

(10)

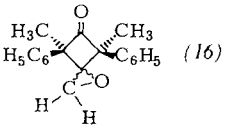

(11)


(12)


(13)


(14)


(15)


(16)

Since the four-membered rings of both *(9)* and *(10)* are subject to stereospecific expansion and undergo neither configurational nor constitutional isomerization we conclude that the resulting "*oxacarbenes*"[10] *are formed directly from the electronically excited four-membered cyclic ketones and not via intermediate 1,4-alkyl/acyl diradicals.*

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[1] 15th Communication on Light-Induced Reactions. This work was supported by Farbwerke Hoechst AG, the Deutsche Forschungsgemeinschaft, and the Fonds der Chemischen Industrie. *P. J.* is grateful to Schering AG for a grant.—14th Communication: *G. Quinkert, B. Bronstert*, and *K. R. Schmieder*, Angew. Chem. *84*, 638 (1972); Angew. Chem. internat. Edit. *11*, 637 (1972).

[2] *W.-D. Stohrer, P. Jacobs, K. H. Kaiser, G. Wiech*, and *G. Quinkert*, Fortschr. Chem. Forsch. *46*, 181 (1974).

[3] *G. Quinkert*, Angew. Chem. *77*, 229 (1965); Angew. Chem. internat. Edit. *4*, 211 (1965); for unequivocal detection of 1,*n*-alkyl/acyl diradicals see ref. [4].

[4] *G. L. Closs* and *C. E. Doubleday*, J. Amer. Chem. Soc. *94*, 9248 (1972); *95*, 2735 (1973); *R. Kaptein*, personal communication.

[5] *G. Quinkert, G. Cimbollek*, and *G. Buhr*, Tetrahedron Lett. *1966*, 4573; *N. J. Turro* and *D. M. McDaniel*, J. Amer. Chem. Soc. *92*, 5727 (1970); *D. M. McDaniel* and *N. J. Turro*, Tetrahedron Lett. *1972*, 3035.

[6] *D. R. Morton* and *N. J. Turro*, J. Amer. Chem. Soc. *95*, 3947 (1973); and further literature cited therein.

[7] *R. Hoffmann*, Accounts Chem. Res. *4*, 1 (1971); and further literature cited therein.

[8] Depending on the bond lengths used, EH model calculations predict the allyl-stabilized diradical to be 0.7 to 0.8 eV more stable than the through-bond coupled diradical.

[9] For experimental details see *P. Jacobs*, Dissertation, Technische Universität Braunschweig 1973.

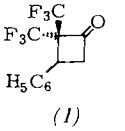
[10] The designation "oxacarbenes" has become accepted for cyclic organo-oxycarbenes.

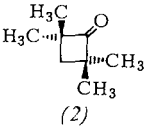
Low Temperature Electronic Spectroscopic Observations on Light-Induced Cyclobutanone-Tetrahydrofurylidene Rearrangement[1]

By *Gerhard Quinkert, Klaus H. Kaiser*, and *Wolf-Dieter Stohrer*[*]

Electronically excited cyclobutanones undergo cycloelimination to ethylene and ketene (or their derivatives), decarbonylation to cyclopropyl compounds, and/or isomerization to ring-expanded oxacarbenes (tetrahydro-2-furylidenes)[2]. The kinetically unstable oxacarbenes can be trapped by alcohols, olefins, or oxygen to give the usual secondary products[3] and thus constitute experimentally well substantiated transients. As C_2 retains the spatial orientation of its ligands on migrating from the C atom to the O atom of the original carbonyl chromophore[4], 1,4-alkyl/acyl diradicals (α-oxo-α,ω-alkylenes) can be ruled out as intermediates during light-induced cyclobutanone-tetrahydrofurylidene isomerization; they do, however, play a plausible role in the genetic interpretation of the structure of cycloelimination and decarbonylation products provided their formation goes with or follows oxacarbene formation. Elucidation of the complex reaction mode of electronically excited four-membered cyclic ketones requires the availability of an experimental method permitting proof of the existence and of subsequent reactions of the oxacarbenes. Since these transients should absorb in the same region as the isoelectronic azo compounds, we have carried out a UV spectroscopic transient analysis using a low temperature technique that has proved of value in other cases[5].

It should be noted that 2,2-bis(trifluoromethyl)-3-phenylcyclobutanone *(1)* gives neither the corresponding acetal at room temperature[6] nor a photoproduct exhibiting maximum electronic absorption around 360 nm[7] at −186 °C in 2-methyltetrahydrofuran (MTHF). On the other hand, many cyclobutanone derivatives which are at least partially converted into acetals on irradiation of their alcoholic solutions lead to a photoproduct, on exposure to light of wavelength >300 nm in MTHF (and sometimes in other solvent glasses) at −186 °C, whose electronic absorption spectrum corresponds to that of (*Z*)-azo compounds[7].


(1)


(2)

The species concerned ought to be oxacarbenes whose kinetic stability depends on the substituents present and on the viscosity of the glass matrix. In some cases[7, 8] the primary tetrahydrofurylidene undergoes thermal conversion into a likewise kinetically unstable secondary intermediate. For example, 2,2,4,4-tetramethylcyclobutanone is rapidly converted into a colorless primary phototransient [λ_{max} = 357 nm in ethanol/isopentane/ether (EPA) = 5:2:5; λ_{max} = 363 nm in methylcyclohexane/3-methylpentane] by 302 nm light at

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−186 °C, which slowly transforms into a red secondary thermo transient (λ_{max} = 437 nm in EPA). The colorless Fluorolube glass permits observation of a broad ESR signal and the red solution shows a well structured signal. Further studies should reveal whether the thermo transient is the 1,4-alkyl/acyl diradical formed from the oxacarbene.

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[1] 16th Communication on Light-Induced Reactions. This work was supported by Farbwerke Hoechst AG, the Deutsche Forschungsgemeinschaft, and the Fonds der Chemischen Industrie.—15th Communication: ref. [4].

[2] *J. C. Dalton* and *N. J. Turro*, Annu. Rev. Phys. Chem. *21*, 499 (1970). The designation "oxacarbenes" has become accepted for cyclic organooxycarbenes.

[3] *P. Yates*, Pure Appl. Chem. *16*, 93 (1968).

[4] *G. Quinkert, P. Jacobs*, and *W.-D. Stohrer*, Angew. Chem. *86*, 197 (1974); Angew. Chem. internat. Edit. *13*, 197 (1974).

[5] *G. Quinkert*, Pure Appl. Chem. *33*, 285 (1973); and further literature cited therein.

[6] *N. J. Turro* and *D. R. Morton*, J. Amer. Chem. Soc. *93*, 2569 (1971).

[7] *W.-D. Stohrer, P. Jacobs, K. H. Kaiser, G. Wiech*, and *G. Quinkert*, Fortschr. Chem. Forsch. *46*, 181 (1974).

[8] *K. H. Kaiser*, Dissertation, Technische Universität Braunschweig 1973.

The Peculiar Behavior of Electronically Excited Cyclobutanones: A Photochemical Example of the Consequence of Through-Bond Interaction[1, 2]

By *Wolf-Dieter Stohrer, Gerhard Wiech*, and *Gerhard Quinkert*[*]

π*,n-Excited common-sized cycloalkanones ($m = 5, 6, 7$) *undergo ring cleavage to 1,m-alkyl/acyl diradicals (α-cleavage)*, while π*,n-excited cyclobutanones ($m = 4$) generally *undergo ring expansion to isomeric oxacarbenes (tetrahydro-2-furylidenes)*[3]. In both cases the photoreaction is initiated by stretching of the C^1—C^m bond. Why do four-membered cyclic ketones behave differently from their higher homologs?

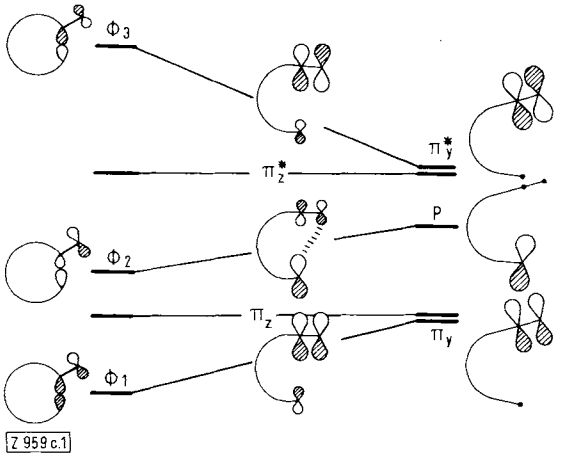


Fig. 1. Correlation diagram for the α-cleavage of a cycloalkanone; the σ orbitals ϕ_1, ϕ_2, ϕ_3 of the ketone which participate in the α-cleavage (or oxacarbene formation) are contructed in a conventional manner from the σ and σ* orbitals of the CC bond to be broken and the n orbital of the oxygen "lone" pair.

The correlation diagram for the α-cleavage of "normal" ketones is depicted in Figure 1. The σ orbitals ϕ_1 and ϕ_3 of the ketone correlate with the acyl orbitals π_y and π_y^* lying in the molecular plane whereas orbital ϕ_2 is transformed into orbital p at C^m. On α-cleavage in the π*,n state the ketone having the configuration $\phi_1^2\pi_z^2\phi_2\pi_z^*$ transforms into the acyl radical of configuration $\pi_y^2\pi_z^2\pi_z^*$ and into the alkyl radical of configuration p. The antibonding character in the C^m—O region of orbital ϕ_2, which is occupied by one electron along the entire reaction coordinate, withstands concerted oxacarbene formation as a competing reaction to α-cleavage.

In the four-membered cyclic ketone special conditions prevail in that the two C atoms are not decoupled on stretching of the C^1—C^4 bond: above a certain C^1—C^4 distance the initially predominating *through-space interaction* is replaced by *through-bond coupling*[4]. Dominance of through-bond coupling is characterized by reversal of the original energy sequence of orbitals ϕ_2 and ϕ_3[4]. This means that the two orbitals tend to cross on cleavage of the C^1—C^4 bond, a true crossing being forbidden by the pseudosymmetry of the system (see Fig. 2).

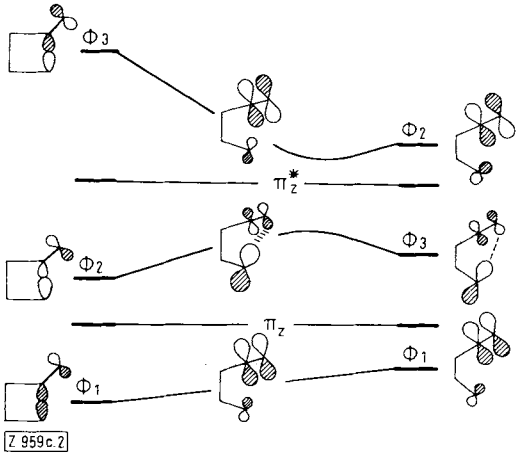


Fig. 2. Correlation diagram for the cleavage of the C^1—C^4 bond in cyclobutanone.

For a small stretching distance C^1—C^4, the highest occupied σ orbital, as in the "normal" ketones (Fig. 1), has ϕ_2 character: the region C^1—C^4 is bonding while C^4—O is antibonding.

For a large stretching distance C^1—C^4 the highest occupied σ orbital has ϕ_3 character: the area important for oxacarbene formation, C^4—O, is bonding and C^1—C^4 is antibonding. These perturbational considerations are confirmed by EH calculations[5] for the correlation diagram of Figure 2[6]. Thus extension of the C^1—C^4 bond in an electronically excited cyclobutanone creates a situation in which the highest (in the π*,n state singly) occupied σ orbital, in contrast to "normal ketones", has bonding character in the region C^4—O and therefore favors oxacarbene formation.

This qualitative MO analysis neither requires a 1,4-alkyl/acyl diradical as an intermediate nor rules such a species out, in contrast to stereochemical studies[3]; everything will depend on the structural scenery in which the transition from a higher to the lowest energy surface takes place (see ref.[7]).

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[2] For previous examples of the chemical consequences of through-bond coupling, see: *R. Hoffmann* and *W.-D. Stohrer*, Spec. Lect. XXIIIrd Int. Congr. Pure Appl. Chem., Vol. *1*, p. 157, Butterworths, London 1971.

[3] *G. Quinkert, P. Jacobs*, and *W.-D. Stohrer*, Angew. Chem. *86*, 197 (1974); Angew. Chem. internat. Edit. *13*, 197 (1974): the designation "oxacarbenes" has become accepted for cyclic organooxycarbenes.

[4] *R. Hoffmann*, Accounts Chem. Res. *4*, 1 (1971); further literature cited.

[5] *R. Hoffmann*, J. Chem. Phys. *39*, 1397 (1963); *40*, 2745 (1964).

[6] *W.-D. Stohrer, P. Jacobs, K. H. Kaiser, G. Wiech*, and *G. Quinkert*, Fortschr. Chem. Forsch. *46*, 181 (1974).

[7] *W.-D. Stohrer, G. Wiech*, and *G. Quinkert*, Angew. Chem. *86*, 200 (1974); Angew. Chem. internat. Edit. *13*, 200 (1974).

A Simple EH Model for the Photochemical Cyclobutanone-Tetrahydrofurylidene Isomerization[1]

By *Wolf-Dieter Stohrer, Gerhard Wiech*, and *Gerhard Quinkert*[*]

The light-induced cyclobutanone-tetrahydrofurylidene isomerization[2] commences with an extension of the C^1—C^4 bond. Beyond a certain stretching distance the ordering of the σ orbitals ϕ_2 and ϕ_3 is reversed[3]. The structural areas before or after this change in orbital sequence belong to the bond or stretch isomers, respectively (see Fig. 1), and the stretching of the C^1—C^4 bond in cyclobutanone is thus a typical example of bond-stretch isomerism[4]. The bonding properties in the stretch isomer *(2) a priori* favor (photochemical) ring closure between centers C^4 and O to afford the corresponding oxacarbene[3].

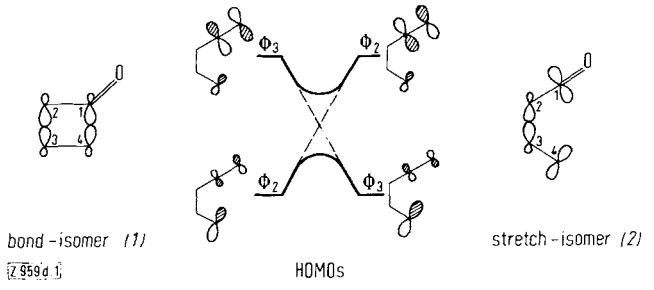
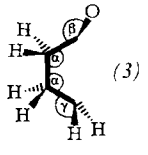


Fig. 1. Behavior of the σ orbitals ϕ_2 and ϕ_3 in "bond-stretch" isomerization.

In order to develop an appreciation of the dynamics of the ligands at C^1 and C^4, which is associated with the bond-stretch isomerism, we have calculated a complete energy surface for the ground state and for the lowest excited state of *(3)* as a function of the degrees of freedom α, β, and γ by the EH method[5].



Curve A—E (Fig. 2) represents the ground state. The transition from *(1)* to *(2)*, formally symmetry-forbidden, by definition causes maximum B. All conformations before this maximum relax to the original reactant A (cf. the nodal properties of ϕ_2); all conformations beyond it (cf. the nodal properties of ϕ_3) relax either to minimum C (1,4-alkyl/acyl diradical) favoring C^1—C^4 interaction by through-bond coupling[6], or to minimum E (oxacarbene) emphasizing through-space interaction between centers C^4 and O. The highest, doubly occupied

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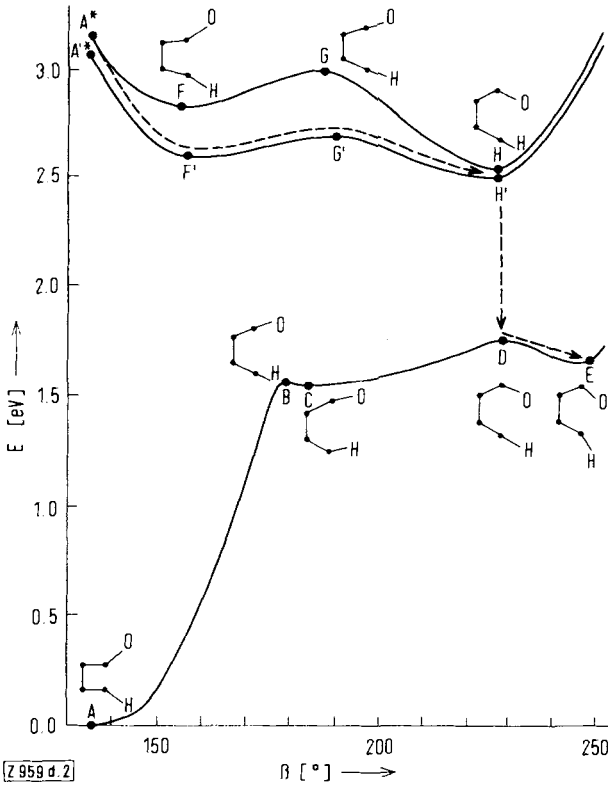


Fig. 2. Vertical sections through calculated energy surfaces: A—E: of the EH ground state; A*—H and A'*—H': of the lowest EH excited state with the O atom in the molecular plane and displaced by 30° from the molecular plane respectively.

orbital ϕ_3 of the 1,4-alkyl/acyl diradical is essentially concentrated on C^4 and the species can be regarded as a carbanion exhibiting pronounced through-bond stabilization[7]. If, in a formal analogy, C^4 in the oxacarbene is defined as a "carbanion" subject to extreme through-space stabilization by interaction with the O atom, then the transition between C and E could be interpreted as inversion of a carbanion. The height of the inversion barrier D would determine the kinetic stability of the oxacarbene.

The points A*—H (Fig. 2) characterize the lowest EH excited state of *(3)* with the O atom in the molecular plane. At minimum F the π^*,n-excited bond isomer has a somewhat longer C^1—C^4 distance than in the ground state, and further extension of this bond causes a considerably shallower rise in energy because the C^1—C^4 bonding orbital is populated by one electron only. The transition from the π^*,n-excited bond isomer to the π^*,n-excited stretch isomer is accompanied—as in the ground state—by an inward displacement of the oxygen towards C^4 ($\beta > 180°$) in order to optimize the stabilizing interaction in the singly occupied orbital ϕ_3; unlike the situation in the ground state the system retains the planar arrangement at C^4. The inward displacement of the oxygen induced by ϕ_3 lowers the energy of the unoccupied orbital ϕ_2 which is concentrated in the carbonyl region where it has antibonding character. The calculations show that at $\beta \approx 190°$ ϕ_2 crosses the hitherto singly occupied π^* orbital, which remains practically unchanged, at G and takes over its electron (Fig. 3).

In this way the deviation, whose inward direction was predetermined, is favored not only by ϕ_3, but initially also by ϕ_2 until the antibonding interaction between C^4 and O, which is weak at first, becomes so strong during the course of displacement that it "stops" the stabilizing displacement at minimum H on the σ^*,n-excited energy surface. Further stabilizing displacement of the O atom towards C^4 is then only possible

if the electron in the C^4—O antibonding orbital ϕ_2 changes to the C^4—O bonding orbital ϕ_3. If this internal conversion ("σ-coupled"[8] transition from H to D) occurs sufficiently

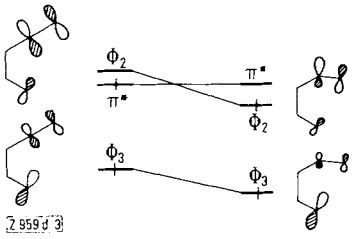


Fig. 3. Energy sequences of the orbitals ϕ_3, π^*, and ϕ_2 of the "stretch" isomer of cyclobutanone for $\beta < ca.\ 190°$ and $\beta > ca.\ 190°$.

rapidly to preclude thermal equilibration at H then the mobile molecule continues its initial motion after reaching D and thus arrives at E[9].

Just as an electron in ϕ_2 favors bending of the three-center system O—C^1—C^2, an electron in the π^* orbital of the CO group of the π*,n-excited cyclobutanone will cause the oxygen to become twisted out of the molecular plane[11]. In order to discover the effect of this tendency on our unrealistic, but transparent model, we have calculated a second energy surface for the lowest EH excited state with the O atom twisted out of the molecular plane by 30°. The new energy curve A'*—H' corresponds qualitatively to that one characterized by A*—H. The lower energy of the former curve is a consequence of σ*π* admixture in the nonplanar system. In this way crossing of the energy surfaces of the "π*,n"- and "σ*,n"-excited stretch isomers is avoided: the crossing point G of the energy surfaces of the π*,n- and σ*,n-excited stretch isomers becomes a true maximum G'.

According to our simple model, the light-induced cyclobutanone-tetrahydrofurylidene isomerization is a diabatic rearrangement in which the oxacarbene is formed in the photochemical primary process[12].

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[1] 18th Communication on Light-Induced Reactions. This work was supported by Farbwerke Hoechst AG, the Deutsche Forschungsgemeinschaft, and the Fonds der Chemischen Industrie. The calculations were performed at the Computing Center of Frankfurt University.—17th Communication: ref. [3].

[2] *D. R. Morton* and *N. J. Turro*, J. Amer. Chem. Soc. *95*, 3947 (1973); and further literature cited therein.

[3] *W.-D. Stohrer*, *G. Wiech*, and *G. Quinkert*, Angew. Chem. *86*, 199 (1974); Angew. Chem. internat. Edit. *13*, 199 (1974); the designation "oxacarbenes" has become accepted for cyclic organooxycarbenes.

[4] *W.-D. Stohrer* and *R. Hoffmann*, J. Amer. Chem. Soc. *94*, 1661 (1972).

[5] *R. Hoffmann*, J. Chem. Phys. *39*, 1397 (1963); *40*, 2745 (1964).

[6] *R. Hoffmann*, Accounts Chem. Res. *4*, 1 (1971); and further literature cited therein.

[7] *R. Gleiter*, *W.-D. Stohrer*, and *R. Hoffmann*, Helv. Chim. Acta *55*, 893 (1972); *P. Buck*, *R. Gleiter*, and *G. Köbrich*, Chem. Ber. *103*, 1431 (1970).

[8] *A. W. J. D. Dekkers*, *J. W. Verhoeven*, and *W. N. Speckamp*, Tetrahedron *29*, 1691 (1973); and further literature cited therein.

[9] Our stereochemical findings rule out that molecules that have arrived at D by internal conversion partition themselves between reaction paths leading to E or C respectively [10].

[10] *G. Quinkert*, *P. Jacobs*, and *W.-D. Stohrer*, Angew. Chem. *86*, 197 (1974); Angew. Chem. internat. Edit. *13*, 197 (1974).

[11] *D. C. Moule*, Can. J. Phys. *47*, 1235 (1969).

[12] For the possible consequences of explicitly accounting for electron-electron interaction see ref. [13].

[13] *W.-D. Stohrer*, *P. Jacobs*, *K. H. Kaiser*, *G. Wiech*, and *G. Quinkert*, Fortschr. Chem. Forsch. *46*, 181 (1974).

Hexakis(trifluorophosphane)vanadium Hydride[1]

By *Thomas Kruck* and *Hans-Ulrich Hempel*[*]

Although trifluorophosphanemetal hydrides are characterized by a considerably greater thermal stability than the carbonylmetal hydrides, which have comparable compositions and structures, corresponding derivatives have so far only been obtained for metals of Groups 7A and 8 (type $HM(PF_3)_5$: M = Mn, Re; type $H_nM(PF_3)_4$: M = Fe, Ru, Os with $n=2$; M = Co, Rh, Ir with $n=1$)[2]. However, the stabilization of transition metal-H bonds by PF_3 ligands provided an early indication that the first hydrido complex *(3)* to be isolated would be a stable vanadium compound HVL_6 in which the central atom could assume the true coordination number 7. Our successful synthesis is based on complete CO/PF_3 exchange on a carbonylmetalate(−I). This preparative finding itself appears remarkable since complete substitution of CO by PF_3 ligands has hitherto only been accomplished with carbonylmetal(0) complexes.

UV irradiation of a solution of bis(diglyme)sodium hexacarbonylvanadate(I) *(1)*[3] in di(2-methoxyethyl) ether (diglyme) saturated with trifluorophosphane afforded an almost quantitative yield of hexakis(trifluorophosphane)vanadate(−I), which is isoelectronic with $Cr(PF_3)_6$ and likewise has an octahedral configuration, in the form of its colorless bis(diglyme)-sodium salt *(2)*.

$$\underset{(1)}{[Na(C_6H_{14}O_3)_2][V(CO)_6]} \xrightarrow[-6CO]{PF_3,\ C_6H_{14}O_3,\ h\nu} \underset{(2)}{[Na(C_6H_{14}O_3)_2][V(PF_3)_6]}$$

$$(2) \xrightarrow{H_3PO_4} \underset{(3)}{HV(PF_3)_6}$$

The composition of *(2)* was established by elemental analysis[4] and by its IR spectrum [ν_{P-F} (cm^{-1}) in KBr: 867 s, 833 vs, 778 s].

The hydrido complex *(3)* can be obtained in almost 70% yield from *(2)* by the action of 90% phosphoric acid and subsequent sublimation at 60 °C/10^{-2} torr. Further sublimation of the product over P_4O_{10} furnishes *(3)* as pale yellow crystals which do not decompose below 135 °C when heated in a sealed tube. The compound is sparingly soluble in saturated hydrocarbons and owing to its strongly acidic character it reacts with oxygen- and nitrogen-containing donor solvents with spontaneous formation of onium salts.

The IR spectrum of gaseous *(3)* contains two bands in the ν_{P-F} region at 911 vs and 846 s cm^{-1} and is thus almost identical with that of hexakis(trifluorophosphane)chromium(0) [ν_{P-F} (gas): 916 vs, 851 s cm^{-1}]. This indicates that hexakis(trifluorophosphane)vanadium hydride has a structure deviating only insignificantly from a regular octahedron.

Further evidence for the presence of a true complex metal hydride comes from the following findings:

1) The substance is diamagnetic[4] having $\chi_m = -236 \times 10^{-6}$ $cm^3\ mol^{-1}$.

2) The mass spectrum[4] (20 eV) displays the molecular ion at *m/e* 580 and fragments derived by successive loss of PF_3 from the ions $HV(PF_3)_5^+$ (*m/e* 492) and $V(PF_3)_5^+$ (*m/e* 491). The absence of $V(PF_3)_6^+$ (*m/e* 579) is remarkable.

3) The ^1H Fourier NMR spectrum[4] of a solution of *(3)* in $Ni(PF_3)_4$ contains a five-line multiplet centered at 18.4 τ; the remaining two of the theoretically predicted seven lines

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are apparently not registered owing to the low solubility of *(3)*.

In addition to $HV(CO)_3(\pi\text{-}C_6H_3(CH_3)_3)$[5] we now have another defined hydrido complex of vanadium in $HV(PF_3)_6$. Whether the above synthetic route is suitable for the preparation of hexakis(trifluorophosphane)metal hydrides of higher homologs of vanadium which may also be capable of existence is currently under study.

Experimental:

All operations are performed under nitrogen; the solvents are purified in the usual way and saturated with nitrogen.

Bis(diglyme)sodium hexakis(trifluorophosphane)vanadate(1) (2)

A solution of *(1)* (7.00 g, 13.7 mmol) in diglyme (150 ml) is cooled to −45 °C and saturated with PF_3 in an irradiation apparatus (Duran 50) with internal cooling and an external vacuum jacket. The vigorously stirred reaction mixture is irradiated for 24 h with an external high-pressure mercury arc lamp (Q 600 Hanau) until evolution of CO is no longer observed. The solution must be resaturated several times with PF_3 during the reaction. The solvent is then removed in a high vacuum and the residue washed twice with light petroleum. The product thus obtained is sufficiently pure for the synthesis of *(3)*. Analytically pure samples are obtained by recrystallizing from diglyme with light petroleum. Yield: 11.64 g (98 %).

Hexakis(trifluorophosphane)vanadium hydride (3)

Compound *(2)* (5.00 g, 5.7 mmol) and crystalline orthophosphoric acid (50 g, 510 mmol) are heated to 60 °C in a flask fitted with a cold trap. The resulting hydrido complex is immediately drawn off into the cold trap (−196 °C) by a high vacuum and then sublimed at 50 °C/10^{-2} torr over P_4O_{10} in order to remove residual traces of water. Yield 2.26 g (68 %) of *(3)*.

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[1] Trifluorophosphanemetal Complexes, Part 46. This work was supported by the Deutsche Forschungsgemeinschaft.—Part 45: *Th. Kruck, H. Jung, M. Höfler,* and *H. Blume*, Chem. Ber., in press.

[2] *Th. Kruck*, Angew. Chem. 79, 27 (1967); Angew. Chem. internat. Edit. 6, 53 (1967).

[3] *R. P. M. Werner* and *H. E. Podall*, Chem. Ind. (London) *1961*, 144.

[4] We are grateful to Dr. *G. Sylvester* and Mrs. *C. Breitkopf* for the magnetic measurements, Dipl.-Chem. *W. Molls*, for recording the mass spectra, Prof. Dr. *H. Günther* and Dipl.-Chem. *H. Schmickler*, for recording the NMR spectra, and to BASF, Ludwigshafen, for the C, H analyses.

[5] *A. Davison* and *D. L. Reger*, J. Organometal. Chem. *23*, 491 (1970).

Doubly Metalated Thiobenzyl Alcohol—Thiobenzaldehyde Dianion[**]

By *Dieter Seebach* and *Karl-Heinz Geiss*[*]

Carbonyl compounds and their analogs always react with nucleophiles (*N*) *(1)* at the C atom. The polarity of this reaction can be reversed in favor of electrophiles (*E*) in the case of dianions *(2)*.

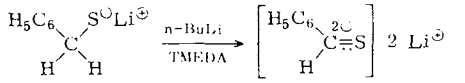
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[**] This work was supported by the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft. We thank *G. Protschuk* for his assistance in a number of experiments.

Dianions of this kind have hitherto been generated exclusively by reaction of carbonyl derivatives with alkali metals[1]. We



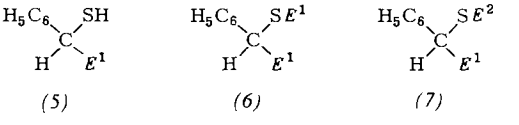
(1) *(2)*



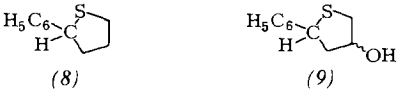
(3) *(4)*

now report the first preparation of such a reagent with X=S by double metalation of the corresponding hydrogenated precursor.

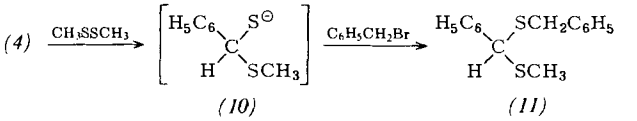
Reaction of a solution of lithium benzyl sulfide *(3)* with *n*-butyllithium, in the presence (2.5 h) or absence (4.0 h) of tetramethylethylenediamine (TMEDA), at −5 °C in THF/pentane (1:1) leads to an orange-colored suspension of the dilithium salt *(4)*. The presence of the dianion is deduced from its reactions with various electrophiles, which we generally add at −78 °C. The products listed in Table 1 can be divided into three different types *(5)*, *(6)*, and *(7)*.



(5) *(6)* *(7)*



(8) *(9)*



(10) *(11)*

1) Thiols of type *(5)* are formed with an aldehyde, a ketone, or trimethylchlorosilane (molar ratio 1:1).

2) Derivatives of type *(6)* are produced with halides, epoxides, or trimethylchlorosilane (molar ratio 1:2).

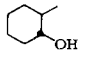
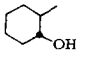
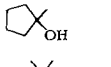
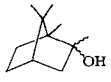
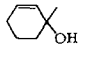
3) Compounds of type *(7)* formed by addition of two different electrophiles to C and S are obtained by consecutive treatment with (i) aldehyde, ketone, or trimethylchlorosilane and (ii) methyl iodide (molar ratio 1:1 in each case).

Special mention should also be made of the tetrahydrothiophenes *(8)* and *(9)* obtainable with 1,3-dibromopropane and epichlorohydrin, respectively, and the mixed dithioacetal *(11)* resulting on benzylation of the primary adduct *(10)* generated with dimethyl disulfide, which is apparently stable under the reaction conditions. Yields (not optimized) and physical data of the derivatives *(5)*—*(9)* and *(11)* are given in Table 1. All the IR and NMR spectra and the results of elemental analysis are in accordance with the structures given. Products having more than one center of asymmetry were isolated as mixtures of diastereoisomers.

Doubly metalated thiobenzyl alcohol is remarkably stable[2]. After storage for two weeks at +5 °C about 30 % of the dianion remains undecomposed. The decomposition products have not yet been studied in detail.

(4) is a readily available, strongly nucleophilic, heterosubstituted carbanion whose reaction products with electrophiles

Table 1. Yields [a] and physical data of the compounds *(5)*—*(9)* and *(11)*.

Product	E^1	E^2	Yield [a] [%]	B.p. [°C/torr] [b] (n_D^{20})
(5)	$(CH_3)_3Si$		73 [c]	43/0.1 (1.5413)
	$C_6H_5C(OH)H$		70	145/0.02 [lit. [d] 150–155/0.04] (1.6096)
(6)	CH_3	CH_3	72	65/2.5 (1.5495; lit. [e] 1.5497
	$(CH_3)_3Si$	$(CH_3)_3Si$	93 [f]	—
	$(CH_3)_2C(OH)CH_2$	$(CH_3)_2C(OH)CH_2$	70	170/0.4 (1.5402)
			80	non-distillable oil
(7)	$(CH_3)_3Si$	CH_3	91	80/0.2 (1.5313)
	n-$C_4H_9C(OH)H$	CH_3	90	110/0.05 (1.5358)
		CH_3	76	130/0.9 (1.5651)
		CH_3	34 [g]	140/0.03
		CH_3	61 [h]	130/0.08
	$C_6H_5C(OH)H$	CH_3	82	160/0.05 (1.6025)
	$(C_6H_5)_2C(OH)$	CH_3	48	m.p. 100.4–101.6°C
(8)			67	100/1.3 (1.5839; lit. [i] 1.5839)
(9)			44	130/0.5 (1.6004)
(11)			73	140/0.03 (1.6195)

[a] Based on distilled or recrystallized product using 10 mmol amounts of starting materials.

[b] Oil bath temperature on molecular distillation.

[c] NMR data identical with those reported in the literature: *A. Wright et al.*, J. Amer. Chem. Soc. *94*, 4784 (1972).

[d] *C. Djerassi et al.*, J. Amer. Chem. Soc. *77*, 568 (1955).

[e] *W. E. Bacon* and *W. M. Le Suer*, J. Amer. Chem. Soc. *76*, 670 (1954).

[f] Determined by spectroscopy; the product very readily loses the *S*-silyl group.

[g] In addition, 45% of a 1:1 mixture of the enolization products (camphor and benzyl methyl sulfide) are obtained.

[h] In addition 14% of the 1,4 adduct are present.

[i] *R. D. Obolentsev* and *V. G. Bukharov*, Chem. Abstr. *55*, 25908b (1961).

are open to a variety of transformations. Preliminary experiments show that other thiols can also be doubly metalated.

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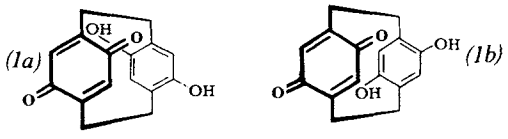
[1] Examples of $(C_6H_5)_2C{=}X$ are
X = O: *P. J. Hamrick* and *C. R. Hauser*, J. Amer. Chem. Soc. *81*, 493 (1959); X = N—C_6H_5: *J. G. Smith* and *R. A. Turle*, J. Org. Chem. *37*, 126 (1972); X = S: *Y. Minoura* and *S. Tsuboi*, J. Org. Chem. *37*, 2064 (1972). There is an otherwise unconfirmed report in the patent literature [*D. O. De Pree* and *J. D. Johnston*, US-Pat. 3239568; Chem. Abstr. *64*, 15921 (1966)] that disodium derivatives can be obtained from aliphatic alcohols and alkylated at carbon.

[2] The formation of 2% of stilbene from thiobenzyl alcohol and potassium *tert*-butoxide in dimethyl sulfoxide at +80°C was explained in terms of an α elimination of the postulated thiobenzyl alcohol dianion: *T. J. Wallace, H. Pobiner, J. E. Hofmann*, and *A. Schriesheim*, J. Chem. Soc. *1965*, 1271.

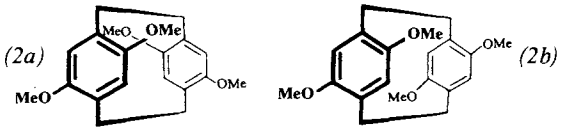
The Pseudogeminal "Quinhydrone" of the [2.2]Paracyclophane Series[1]

By *Walter Rebafka* and *Heinz A. Staab*[*]

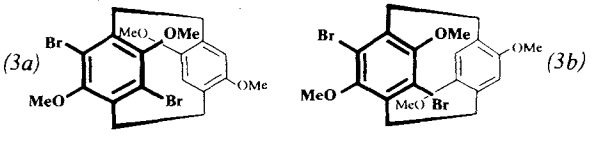
For the investigation of intramolecular donor-acceptor interactions a comparison of the two stereoisomeric "quinhydrones" *(1a)* and *(1b)* of the [2.2]paracyclophane series[2] was thought to be promising: although the total electron affinity of the acceptor and the total ionization energy of the donor are the same in *(1a)* and *(1b)* the sterical conditions for π-electron overlap and the differences of charge densities on opposite carbon atoms are characteristically different in the two systems. Therefore some information about the importance of sterical factors and of local conditions to donor-acceptor interactions was to be expected.



Synthesis and properties of the pseudoortho compound *(1a)* have been reported recently[1]. The pseudogeminal stereoisomer *(1b)* was not obtainable in an analogous reaction sequence since ring contraction of *both* diastereomeric 5,8,14,17-tetramethoxy-2,11-dithia[3.3]paracyclophanes using three different methods yielded only the chiral 4,7,12,15-tetramethoxy[2.2]paracyclophane *(2a)*[1] but not the achiral pseudogeminal *(2b)*. The exclusive formation of *(2a)* with the sterically more favored arrangement of the four methoxy groups is explained on the assumption that a two-step radical mechanism of the three ring-contraction methods allows formation of the thermodynamically more stable stereoisomer by the rotation of an aryl unit through 180°[3]. On the basis of this assumption the following synthesis of *(2b)* was developed.

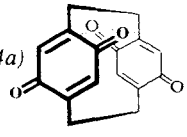
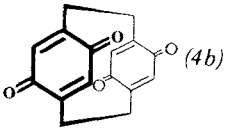


Treatment of 1,4-dibromo-2,5-dimethoxy-3,6-dimethylbenzene[4] (prepared from 1,4-dimethoxy-2,5-dimethylbenzene[5] by electrophilic bromination, 80%, m.p. 125–126°C) with *N*-bromosuccinimide/carbon tetrachloride yielded 1,4-dibromo-2,5-dimethoxy-3,6-bis(bromomethyl)benzene[4] (85%, m.p. 194–195°C) which was cyclized with 1,4-bis(mercaptomethyl)-2,5-dimethoxybenzene to give 5,8-dibromo-6,9,14,17-tetramethoxy-2,11-dithia[3.3]paracyclophane[4] (conditions cf.[1], 7–15%, m.p. 235–237°C)[6]. By irradiation in triethyl phosphite (450-W Hg high-pressure lamp, 16 h) a mixture of both stereoisomeric 4,7-dibromo-5,8,12,15-tetra-



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methoxy[2.2]paracyclophanes *(3a)* and *(3b)* was obtained (total yield 35–40%), the now sterically favored *(3b)* with pseudogeminal arrangement of the four methoxy groups prevailing in the ratio of about 2:1. *(3a)*[4] (m. p. 137–138 °C) and *(3b)*[4] (m. p. 157–159 °C) were separated by chromatography (silica gel; benzene/CCl_4, 2:1). Halogen-metal exchange of *(3b)* with *n*-butyllithium (ether/*n*-hexane) and hydrolysis yielded *(2b)*[4] [56%, m. p. 229–230 °C; ^{1}H-NMR ($CDCl_3$): τ=4.15 (s, 4 arom. H), 7.6—6.35 (AA'BB', 8 methylene-H)] whereas the corresponding reaction with *(3a)* led to *(2a)*[1]. Demethylation of *(2b)* and oxidation of the intermediate tetrahydroxy[2.2]paracyclophane to the bis-quinone *(4b)* were carried out according to the corresponding steps of the synthesis of *(4a)*[1] with slight modifications because of the low solubility of the pseudogeminal compounds (60% yield). The pseudogeminal structure of *(4b)*[4] (yellow needles, dec. >200 °C) was confirmed by X-ray analysis[7] [^{1}H-NMR (CF_3COOH): τ=3.44 (s, 4 ring-H), 7.55—6.08 (m, 8 methylene-H); MS: M^+ 268, fragmentation similar to *(4a)*[1]].

(4a)   *(4b)*

Catalytic hydrogenation of *(4b)* (Pd/C, 1 equiv. H_2, dioxane) and subsequent recrystallization from dioxane gave *(1b)* as black crystals [(dec. >350 °C, 75% yield)[4]; MS: M^+ found 270.0898, calc. 270.0891; ^{1}H-NMR ([D_6]-dimethyl sulfoxide): τ=6.5—8.0 (m, 8 methylene-H), 4.14 and 3.98 (singlets for 2 ring-H each), 1.30 (s, 2 hydroxyl-H)]. In contrast to that of *(1a)*[1] the IR spectrum (KBr) of *(1b)* shows a very broad ν(OH) absorption around 3200 cm^{-1} and a ν(CO) absorption shifted to 1620 cm^{-1}, indicating strong hydrogen bonds.

Apart from UV absorptions at 246 (ε 9.350), 277 (5.150), and 320 nm (3.200), *(1b)* exhibits a typical broad charge-transfer absorption between 400 and 600 nm similar to *(1a)* (λ_{max} 500 nm). However, its extinction ($\varepsilon \approx 1.700$, in methanol) is ten times higher than for the corresponding band of *(1a)*. In contrast to *(1a)*, the ^{1}H-NMR of which shows no change up to 200 °C (in [D_6]-dimethyl sulfoxide), a reversible coalescence of the singulets at τ=4.14 and 3.98 is observed for *(1b)* at 160 °C in the same solvent. Obviously this coalescence is the result of an exchange of oxidation states between the two rings with simultaneous proton transfer ($\Delta G^{\neq}_{160\,°C} \approx 22.2$ kcal/mol).

The "intramolecular quinhydrones" *(1a)* and *(1b)* as well as the bis-quinones *(4a)* and *(4b)* form paramagnetic anions in which according to ESR measurements a fast electron exchange between both rings takes place[8].

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[1] Transannular Interactions in [2.2]Phanes, Part 5.—Part 4: *W. Rebafka* and *H. A. Staab*, Angew. Chem. *85*, 831 (1973); Angew. Chem. internat. Edit. *12*, 776 (1973).

[2] First attempts to prepare these "exotic quinhydrones" were discussed by *D. J. Cram* and *A. C. Day*, J. Org. Chem. *31*, 1227 (1966).

[3] Cf. *H. A. Staab* and *M. Haenel*, Chem. Ber. *106*, 2190 (1973); *M. Haenel* and *H. A. Staab*, *ibid. 106*, 2203 (1973).

[4] Correct elemental analyses were obtained for these compounds; ^{1}H-NMR and mass spectra as well as other spectroscopic results are in accordance with the structures proposed.

[5] 1,4-Dimethoxy-2,5-dimethylbenzene was obtained from 1,4-dimethoxybenzene by chloromethylation and subsequent hydrogenolysis ($LiAlH_4$/tetrahydrofuran) in 47% overall yield.

[6] In this reaction only one of the two possible stereoisomeric dithia[3.3]paracyclophanes—most probably the compound with pseudogeminal arrangement of the methoxy groups—was obtained.

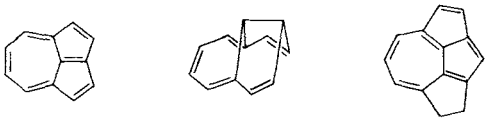
[7] *(4b)* crystallizes in space group $P2_1/n$ with two molecules in the unit cell (a=7.930, b=9.280, c=8.024 Å, β=93.30°); the molecules are placed on centers of symmetry and therefore must be centrosymmetric themselves (*H. Irngartinger*, unpublished).

[8] *J. Valenzuela*, *F. A. Neugebauer*, *W. Rebafka*, and *H. A. Staab*, unpublished.

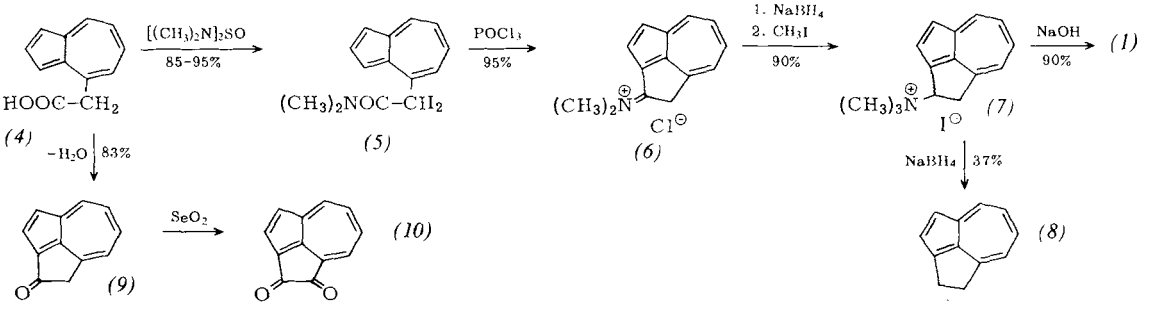
Cyclopent[*cd*]azulene and 1,2-Dihydrodicyclopent-[*cd,ij*]azulene

By *Klaus Hafner*, *Klaus-Peter Meinhardt*, and *Winfried Richarz*[*]

Alkyl and aryl derivatives[1] of cyclopent[*cd*]azulene *(1)* exhibit a notable reactivity in cycloaddition reactions with alkenes, alkynes, and carbenes[2]. An examination of the hitherto unknown parent hydrocarbon *(1)* therefore appeared desirable. The 2a,8b-dihydro derivative *(2)* has recently been prepared by *Paquette et al.*[3] and by *Vogel et al.*[4]. We wish to report a simple synthesis of *(1)* and of 1,2-dihydrodicyclopent[*cd,ij*]azulene *(3)* which is likewise characterized by a pronounced reactivity of the double bonds in its five-membered rings.



(1) *(2)* *(3)*

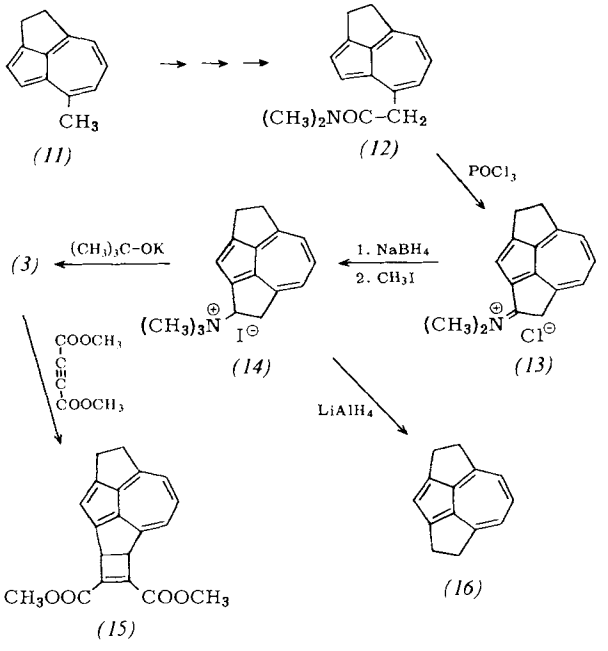


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4-Azulenylacetic acid *(4)* (m.p. 122 °C, decomp.)[5], prepared in 75% yield by reaction of 4-methylazulene[6] with sodium *N*-methylanilide and subsequent carboxylation of the resulting sodium 4-methyleneazulenide[7], proved to be useful as starting material for the synthesis of *(1)*. By treatment with sulfinylbis-(dimethylamine)[8] in benzene for 2h at 60 °C *(4)* can be converted almost quantitatively into the carboxamide *(5)*. Cyclization in $POCl_3$ (60 °C, 2 h) yields 95% of the ketimonium chloride *(6)* (perchlorate: red-brown crystals, m.p. 243 to 244 °C, decomp.). Reduction of *(6)* by $NaBH_4$ in methanol at 20 °C followed by quaternization with methyl iodide affords the iodide *(7)* (yield 90%; blue-violet crystals, decomp. >110 °C), and Hofmann degradation with 2 N NaOH at 20 °C finally gives rise to a 90% yield of the hydrocarbon *(1)* (brown leaflets having metallic luster, m.p. 69—70 °C, decomp.). Compound *(1)* is yellowish brown in solution and prone to autoxidation but thermally stable.

The 60 MHz ^{1}H-NMR spectrum of *(1)* (in CCl_4), which provides structural proof for the compound, contains a multiplet centered at $\tau = 1.93$ for the four protons of the seven-membered ring in addition to the signals of the two AB systems for the protons of the five-membered rings at $\tau = 3.18$ and 2.54 ($J_{AB} = 4.5$ Hz). The electronic spectrum of *(1)* (in *n*-hexane) shows a pronounced vibrational structure in the UV and visible regions.

Reduction of the quaternary salt *(7)* by $NaBH_4$ in methanol at 0 °C yields 1,2-dihydrocyclopent[*cd*]azulene *(8)* (yield 37%; dark blue needles, m.p. 71 °C) which is isomeric to *(2)* and whose 2-oxo derivative *(9)* is accessible by direct cyclization of *(4)* in acetic anhydride/pyridine (yield 83%; red-brown crystals, m.p. 131—132 °C). Oxidation of *(9)* with selenium dioxide in dioxane (60 °C, 3h) affords cyclopent[*cd*]azulene-1,2-dione *(10)* (10% yield, dark green needles, decomp. >240 C), an isomer of acenaphthenequinone.



Compound *(3)* was prepared similarly to *(1)* starting from 4,8-dimethylazulene[6]. 5-Methyl-1,2-dihydrocyclopent[*cd*]-azulene *(11)* (blue needles, m.p. 132 °C) obtained analogously to *(8)* is converted into the carboxamide *(12)* (yield 95%; blue rhomboids, m.p. 115 °C) which is cyclized to the tetracyclic ketimonium salt *(13)* (yield 45%; perchlorate: red-brown needles, decomp. >270 °C). Reduction ($NaBH_4$) and quaternization with methyl iodide finally yield the iodide *(14)* (air-sensitive blue powder). Treatment of *(14)* with potassium *tert*-butoxide in tetrahydrofuran at −20 °C furnishes the highly strained, thermally unstable tetracyclic hydrocarbon *(3)* which is yellowish green in solution and could hitherto only been trapped as the cycloadduct *(15)* (dark green crystals, m.p. 108 °C) by reaction with dimethyl acetylenedicarboxylate at 0 °C. Reduction of *(14)* by lithium tetrahydridoaluminate in ether at 20 °C affords 1,2,4,5-tetrahydrodicyclopent[*cd,ij*]-azulene *(16)* as pale blue needles (m.p. 180 °C, decomp.; yield 85%).

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[1] *K. Hafner* and *J. Schneider*, Liebigs Ann. Chem. *624*, 37 (1959); *K. Hafner* and *K. F. Bangert*, *ibid.* *650*, 98 (1961); *K. Hafner*, Angew. Chem. *75*, 1041 (1963); Angew. Chem. internat. Edit. *3*, 165 (1964); *K. Hafner*, Pure Appl. Chem. *28*, 153 (1971).

[2] *K. Hafner* and *R. Fleischer*, Angew. Chem. *82*, 217 (1970); Angew. Chem. internat. Edit. *9*, 247 (1970); *K. Hafner* and *W. Rieper*, Angew. Chem. *82*, 218 (1970); Angew. Chem. internat. Edit. *9*, 248 (1970).

[3] *L. A. Paquette*, *R. A. Wingard, Jr.*, and *R. K. Russell*, J. Amer. Chem. Soc. *94*, 4739 (1972); *G. P. Ceasar*, *J. Green*, *L. A. Paquette*, and *R. E. Wingard, Jr.*, Tetrahedron Lett. *1973*, 1721.

[4] *E. Vogel*, *U. H. Brinker*, *K. Nachtkamp*, *J. Wassen*, and *K. Müllen*, Angew. Chem. *85*, 760 (1973); Angew. Chem. internat. Edit. *12*, 758 (1973).

[5] The structures of the products described were confirmed by elemental analysis, and UV, NMR, and MS spectra.

[6] *K. Hafner* and *H. Weldes*, Liebigs Ann. Chem. *606*, 90 (1957).

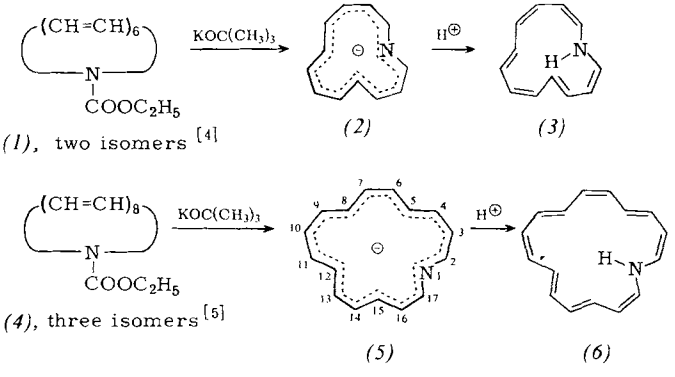
[7] Cf. *K. Hafner*, *H. Pelster*, and *H. Patzelt*, Liebigs Ann. Chem. *650*, 80 (1961).

[8] *G. Rosini*, *G. Baccolini*, and *S. Cacchi*, Farmaco, Ed. Sci. *26*, 153 (1971).

An Aza[13]- and an Aza[17]annulenyl Anion[1][**]

By *Gerhard Schröder*, *Günter Frank*, *Herbert Röttele*, and *Jean F. M. Oth*[*]

The pyrrolyl or aza[5]annulenyl anion has long been known and possesses considerable interest from both a theoretical and a preparative standpoint[2]. The synthesis and properties of the azoninyl or all-*cis*-aza[9]annulenyl anion have recently been described[3]. We now wish to report an aza[13]- *(2)* and an aza[17]annulenyl anion *(5)*.



Photolysis of the adduct of ethoxycarbonylnitrene to the double bond of the four-membered ring in tricyclo[6.4.0.0^{9,12}]dodeca-2,4,6,10-tetraene at −70 °C affords two isomeric *N*-

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[**] We are grateful to Badische Anilin- & Soda-Fabrik AG, Ludwigshafen, for a gift of cyclooctatetraene.

ethoxycarbonylaza[13]annulenes *(1)*[4]. Photolysis of the addition product of ethoxycarbonylnitrene to tricyclo-[8.6.0.0^{2,9}]hexadeca-3,5,7,11,13,15-hexaene leads to three isomeric *N*-ethoxycarbonylaza[17]annulenes *(4)*[5].

Treatment of the azaannulenes *(1)* and *(4)* respectively with potassium *tert*-butoxide in THF at 0 °C alway furnishes the same aza[13]- and aza[17]annulenyl anions, according to NMR spectroscopic evidence. On the basis of the NMR spectra (see Table 1) and double resonance experiments considering in particular the number of inner and outer protons, the characteristic absorptions of the protons in α and β position to the nitrogen, and the coupling constants, these anions must be assigned the configurations *(2)* and *(5)*[6] respectively.

The following three points warrant attention:

1) The configurationally isomeric azaannulene *(1)* or *(4)* gives rise to only one azaannulenyl anion, *(2)* or *(5)*. We thus conclude that the aza[13]- and the aza[17]annulenyl anions must be configurationally labile.

2) The nonbonding electron pair on the nitrogen of *(2)* and *(5)* is directed towards the center of the ring. Taking account of the statements made under 1, we deduce that the spatial requirement of a hydrogen on the sp^2 C atom is greater than that of the lone pair of the sp^2 N atom.

3) The difference between the resonance signals for the inner and outer protons is *ca.* 10 ppm for *(2)* and *ca.* 14 ppm for *(5)*. These values indicate that the magnetic field induces a considerable diamagnetic ring current in these species.

Protonation of *(2)* and *(5)* with water-saturated ether containing a small amount of acetic acid yields crystals of aza[13]-*(3)* and aza[17]annulene *(6)*, respectively, which decompose on attempted melting-point determination. The compounds were purified by column chromatography [*(3)*: Al_2O_3 (basic); *(6)*: SiO_2 (pentane/ether 95:5)]; they are highly sensitive to oxygen. The configurations *(3)* and *(6)* are unequivocally confirmed by NMR data (see Table 1) and by the following experiment: If a solution of *(3)* or *(6)* in CS_2 is shaken with D_2O in a NMR sample tube, the intensities of the upfield signals at τ = 7.20 and 8.5 respectively are each reduced by about 1 H.

We assign the upfield signals in the ^{1}H-NMR spectrum of *(3)* and *(6)* to the inner protons, and the downfield signals to the outer protons. The difference in the center of gravity of these signals amounts to *ca.* 4.7 ppm for *(3)* and *ca.* 5 ppm for *(6)*. The induced diamagnetic ring current is now considerably smaller than in *(2)* and *(5)*, but, unlike that in *(1)*[4] and *(4)*[5], it is however still readily detectable. This finding accords with previous results for aza[9]annulenes[3].

Table 1. Data of *(2)*, *(3)*, *(5)*, and *(6)*.

Cpd.	Yield [%]	^{1}H-NMR, τ [ppm] [a]
(2) red-brown	≈ 100 [b]	0.45 (1α-H/d; J = 7 Hz), 0.58 (1α-H/d; J = 7.5 Hz), 1.90 (4 H/m), 2.60 (1 H/t; J = 9 Hz), 2.72 (1 H/t; J = 10.5 Hz), 3.08 (1 β-H/t; J = 7 Hz), 3.24 (1 β-H/dd, J = 7.5/10.5 Hz), 12.27 (1 H/t; J = 13.5 Hz), 13.05 (1 H/t; J = 14 Hz)
(3) yellow	≈ 80 [b]	2.72 (1 α-H/d; J = 8.5 Hz), 2.8—3.8 (7 H/m), 4.34 (1 β-H/dd; J = 6.5/8.5 Hz), 4.55 (1 β-H/t; J = 8.5 Hz), 7.20 (1 N—H/br. s), 7.71 (1 H/t; J = 13 Hz), 7.99 (1 H/dd; J = 11/17.5 Hz)
(5) blue-green	≈ 100 [c]	−0.35 (2 α-H/two d; J = 6/7 Hz), 0.5—1.1 (7 H/m), 1.40 (1 β-H (16-H)/d,d; J = 6/13 Hz), 2.05 (1 H (10-H/t; J = 10 Hz), 2.70 (1 β-H (3-H)/d,d; J = 7/10 Hz), 14.9 (4 H/four t; J = 13 Hz)
(6) red	≈ 60 [c]	2.2—3.0 (9 H/m) [d], 3.25 (1 β-H/d,d; J = 8/11 Hz), 3.45 (1 β-H/d,d; J = 8/13 Hz), 4.24 (1 H (10-H)/t; J = 8.5 Hz), 7.55 (1 H/t; J = 13 Hz), 7.98 (1 H/d,d; J = 10.5/14.5 Hz), 8.5 (3 H/m, one of which is 1 H N—H, see text)

[a] 100 and 60 MHz spectra, *(2)* and *(5)* in THF, *(3)* and *(6)* in CS_2; *ca.* 25 °C; TMS as standard.
[b] Based on *(1)*.
[c] Based on *(4)*.
[d] The two α protons appear as two doublets at τ = 1.95 in D_8-THF at −60 °C.

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[1] Annulenes, Part 22.—Part 21: *G. Schröder, G. Kirsch,* and *J. F. M. Oth*, Chem. Ber. *107*, 460 (1974).

[2] See, *e.g., M. H. Palmer:* The Structure and Reactions of Heterocyclic Compounds. E. Arnold, London 1967.

[3] *A. G. Anastassiou*, Accounts Chem. Res. *5*, 281 (1972); *A. G. Anastassiou* and *S. W. Eachus*, J. Amer. Chem. Soc. *94*, 2537 (1972); *R. T. Seidner* and *S. Masamune*, J. C. S. Chem. Comm. *1972*, 149.

[4] *G. Schröder, G. Frank,* and *J. F. M. Oth*, Angew. Chem. *85*, 353 (1973); Angew. Chem. internat. Edit. *12*, 328 (1973).

[5] *G. Schröder, G. Heil, H. Röttele,* and *J. F. M. Oth*, Angew. Chem. *84*, 474 (1972); Angew. Chem. internat. Edit. *11*, 426 (1972).

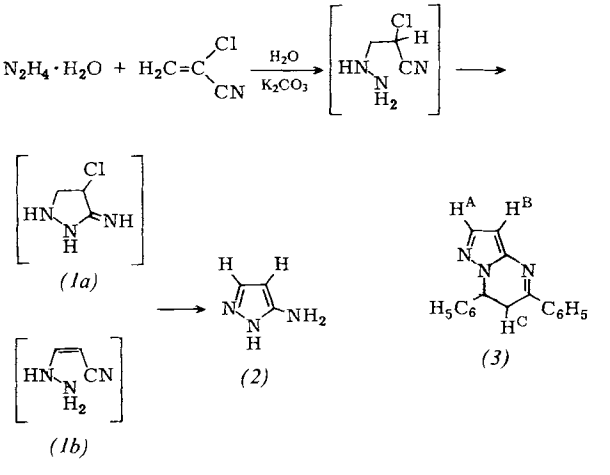
[6] We cannot rule out a positional isomer of *(5)* in which the nitrogen shows up at position 5 (retaining the numbering given in *(5)*).

A Simple Synthesis of 3(5)-Aminopyrazole[**]

By *Günter Ege* and *Philipp Arnold*[*]

Dedicated to Professor Hans Plieninger on the occasion of his 60th birthday

3(5)-Aminopyrazole has formerly been accessible only by way of multistage syntheses[1-3]. We now report a one-stage preparation of 3(5)-aminopyrazole *(2)* utilizing commercially available starting materials and giving 70% yields of the pure product. The reaction involves addition of aqueous hydrazine solution to 2-chloroacrylonitrile in alkaline solution (potassium carbonate).



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Extraction with ethyl acetate or ether and distillation of the crude oil[4] furnishes pure *(2)*. As shown in the reaction scheme, the overall reaction proceeds *via* several unisolated intermediates and it has not yet been established whether the cyclization occurs with *(1a)* or *(1b)*. Remarkably, in the present synthesis, ring closure takes place in alkaline solution whereas comparable cyclizations invariably have to be performed in acidic media[2, 5]. Like other aminoazoles having a 2-aminopyrrole structure, compound *(2)* reacts with 1,3-dicarbonyl compounds to give pyrazolo[2,3-*a*]pyrimidines *(3)*[6].

3(5)-Aminopyrazole (2)

Hydrazine hydrate (55 g, 1.1 mol) is added to a solution of K_2CO_3 (140 g, 1 mol) in water (400 ml). To this vigorously stirred mixture is then added dropwise 2-chloroacrylonitrile[7] (87.5 g, 1 mol) at 5—10 °C (ice-salt cooling) under nitrogen over a period of 1 h. Stirring is continued for 1 h at room temperature and 1.5 h at 40—50 °C, and the mixture left to stand overnight. Extraction for 24 h with ethyl acetate[8] and vacuum distillation of the residual crude oil (75 g, 90 %) under nitrogen affords 58 g (70 %) of *(2)*, b. p. 120—122 °C/0.3 torr. Compound *(2)* solidifies on cooling, preferably with seeding (m. p. 36 °C). The IR spectrum accords with that of authentic 3(5)-aminopyrazole[2]. Picrate: m. p. 222 °C from methanol.

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[1] *H. Reimlinger, A. van Overstraeten,* and *H. G. Viehe,* Chem. Ber. *94*, 1036 (1961).

[2] *H. Dorn* and *A. Zubek,* Org. Synth. *48*, 8 (1968).

[3] *K. J. Klebe* and *C. L. Habraken,* Synthesis *1973*, 294.

[4] The IR spectrum shows that this crude oil is cyclized *(2)*.

[5] Substituted enehydrazino nitriles are known, and cyclize in acidic media to give aminopyrazoles; cf. *A. Takamizawa* and *S. Hayashi,* Jap. Pat. *1970*, 26082; Chem. Abstr. *74*, 3617 v (1971).

[6] Cf., *e.g., R. C. Elderfield:* Heterocyclic Compounds. Vol. 8. Wiley, New York 1967, p. 61; *Y. Makisumi,* Chem. Pharm. Bull. *10*, 612 (1962); Chem. Abstr. *58*, 13949 f (1963); compound *(3)* was obtained in 80 % yield in the form of yellowish green crystals (m. p. 85—86 °C) on boiling of *(2)*, dibenzoylmethane, and catalytic quantities of *p*-toluenesulfonic acid in benzene; ^{1}H-NMR spectrum of *(3)* ($CDCl_3$): $\delta = 6.78$ (d, $J = 2.3$ Hz, H^B), 7.3 to 8.2 (m, aromatic H, H^A and H^C, the last two being obliterated by the aromatic H); UV (CH_2Cl_2): $\lambda_{max} = 269$ nm ($\varepsilon = 40000$), 318 (6500), 355 (3800).

[7] We are grateful to the Münzing company, 71 Heilbronn/Neckar (Germany), for a gift of 2-chloroacrylonitrile.

[8] Rotary perforator designed by *Ludwig* and produced by Otto Fritz GmbH, 6238 Hofheim/Taunus (Germany). Extraction with ether requires *ca.* 50 h; however, a smaller residue is then obtained on vacuum distillation.

Reaction of *cis*-Bicyclo[6.1.0]nona-2,4,6-triene with Tetracyanoethylene[**]

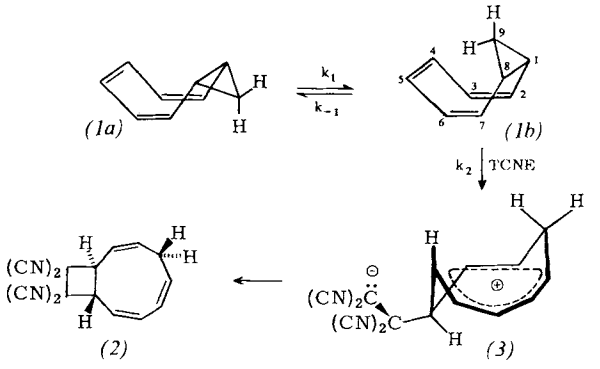
By *Gernot Boche, Heinrich Weber,* and *Jürgen Benz*[*]

cis-Bicyclo[6.1.0]nona-2,4,6-triene *(1)* reacts with tetracyanoethylene (TCNE) to form the *trans*-linked 1:1 adduct *(2)*[1, 2]. In a detailed study of electrophilic addition reactions to *cis*-bicyclo[6.1.0]nonatriene the formation of *(2)* was formulated as involving attack by TCNE on C^3 of the coiled conformation *(1b)*. The *exo*-3-*trans*-1,3-bishomotropylium zwitterion *(3)* was postulated as intermediate[2, 3].

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Since conformational equilibration *(1a)*⇌*(1b)* is certainly rapid the bimolecular reaction *(1b)* + TCNE $\xrightarrow{k_2}$ *(3)* would represent the rate-determining step of such a mechanism. Hence the pseudo-first order rate constant k_{exp} determined



experimentally with an excess of TCNE should be a linear function of the TCNE concentration.

We have performed a kinetic study of the reaction of *(1)* (0.085 mol/l) with TCNE (6—25 mol. equiv.) in acetonitrile (CH_3CN), tetrahydrofuran (THF), and CH_3CN/THF (1:1) at 31.3 °C. Figure 1 shows a plot of k_{exp} *versus* increasing TCNE concentration.

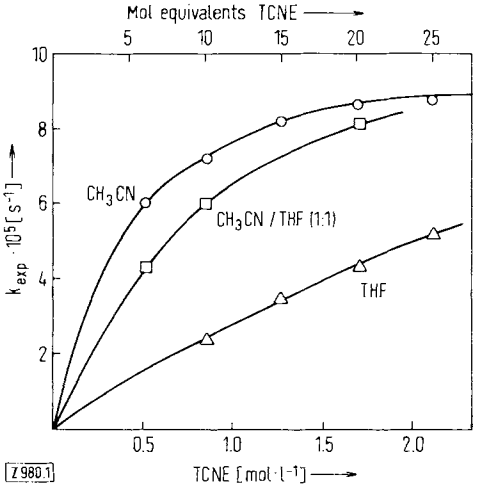
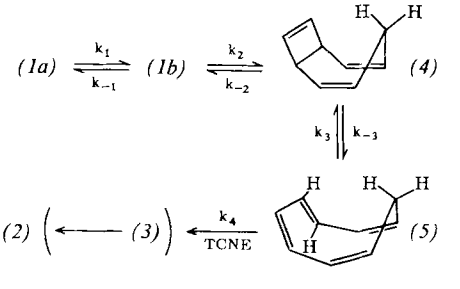


Fig. 1. Rate constant k_{exp} for the reaction of *(1)* with TCNE in various solvents at 31.3 C *vs.* TCNE concentration.

Since the k_{exp} values do not vary in a linear fashion with the TCNE concentration but instead tend to a plateau value, a direct reaction of *(1)* with TCNE can be ruled out.

The kinetic data do however indicate a reaction course in which cycloaddition to TCNE is preceded by a rate-determining valence isomerization of *(1)*[4]. In the reaction sequence formulated below, in which *cis*-bicyclo[6.1.0]nonatriene *(1)*



is in equilibrium with bicyclo[5.2.0]nona-2,5,8-triene *(4)* and the latter in turn with *cis,trans,cis,cis*-cyclononа-1,3,5,7-tetraene *(5)*[5], the Cope rearrangement *(1b)*⇌*(4)* should be fast and the valence isomerization *(4)*⇌*(5)* slow[6]. Compound *(5)*, which could also be trapped in a Diels-Alder reaction[7], then reacts with TCNE.

The rate constant k_{exp} of this scheme can be expressed by

$$k_{exp} = K \times k_3 - \frac{k_{-3}}{k_4} \times \frac{k_{exp}}{[TCNE]} \quad (1)$$

where K is the rate constant between *(1a)* and *(4)*. In accord with eq. (1), a plot of k_{exp} *versus* $k_{exp}/[TCNE]$ now gives a straight line of slope k_{-3}/k_4 which intersects the ordinate at $K \times k_3$[4].

Further confirmatory evidence comes from the ratio $k_{exp}(CH_3CN) : k_{exp}(THF)$ with, *e.g.*, 25 equiv. of TCNE, which amounts to only 1.7 (see Fig. 1). This almost negligible solvent dependence is hardly reconcilable with the formation of the zwitterion *(3)* in the rate-determining step.

Our kinetic findings are therefore plausible when *cis,trans,-cis,cis*-cyclononatetraene *(5)* is assumed as reactive intermediate.

Can we summon any additional evidence that *(5)* isomerizes to *(1)* and reacts with TCNE to give *(2)*, and that the cycloaddition *(5)*+TCNE competes successfully with the isomerization *(5)*→*(1)*?

We were able to produce *(5)* by protonation of the *cis,cis,cis,-trans*-[9]annulene anion[8]. At −28 °C it is transformed with a half-life of 34 min into *(1)*. However, if *(5)* is allowed to react with TCNE in dimethyl ether at −50 °C then the cycloadduct *(2)* is formed. In contrast, *(1)* does not react under these conditions.

The agreement between these experiments and the kinetic findings in various solvents reveals that the highly strained *cis,trans,cis,cis*-cyclononatetraene *(5)* assumes the role of reactive intermediate in the reaction of *cis*-bicyclo[6.1.0]nonatriene *(1)* with TCNE[10]. In the (2+2) cycloaddition of *(5)*, the zwitterion *(3)* represents a possible but not a necessary intermediate.

Received: October 22, 1973;
In shortened form: November 7, 1973 [Z 980 IE]
German version: Angew. Chem. 86. 238 (1974)

[1] *T. J. Katz* and *P. J. Garratt*, J. Amer. Chem. Soc. *86*, 5194 (1964); *G. Boche* and *W. E. Konz*, unpublished results 1966; *W. H. Okamura* and *T. W. Osborne*, J. Amer. Chem. Soc. *92*, 1061 (1970); *C. S. Baxter* and *P. J. Garratt*, *ibid. 92*, 1062 (1970); Tetrahedron *27*, 3285 (1971).

[2] *L. A. Paquette, M. J. Broadhurst, L. K. Read*, and *J. Clardy*, J. Amer. Chem. Soc. *95*, 4639 (1973); *94*, 2904 (1972).

[3] *L. A. Paquette, M. J. Broadhurst, C. Lee*, and *J. Clardy*, J. Amer. Chem. Soc. *95*, 4647 (1973); *94*, 630, 632 (1972).

[4] Cf.: *R. Huisgen* and *F. Mietzsch*, Angew. Chem. *76*, 36 (1964); Angew. Chem. internat. Edit. *3*, 83 (1964).

[5] The equilibrium *(1)*⇌*(4)*⇌*(5)* has been discussed earlier: *S. W. Staley* and *T. J. Henry*, J. Amer. Chem. Soc. *91*, 1239, 7787 (1969); *J. E. Baldwin, A. H. Andrist*, and *R. K. Pinschmidt*, *ibid. 94*, 5845 (1972); *W. Grimme*, *ibid. 95*, 2381 (1973); cf. also ref. [7].

[6] Cf.: *G. Maier*: Valenzisomerisierungen. Verlag Chemie, Weinheim 1972, pp. 89ff.; *W. Grimme* and *K. Seel*, Angew. Chem. *85*, 514 (1973); Angew. Chem. internat. Edit. *12*, 507 (1973).

[7] *A. G. Anastassiou* and *R. C. Griffith*, J. Amer. Chem. Soc. *93*, 3083 (1971).

[8] In addition to *(5)*, protonation of the *cis,cis,cis,trans*-[9]annulene anion also yields all-*cis*-cyclononatetraene and the *trans,cis,cis,cis* isomer. The latter isomerizes at −30 °C to *trans*-dihydroindene and reacts with TCNE at −60 °C to give a bicyclic adduct, m.p. 153—154 °C. The stereochemistry of the ring linkage is unknown [9].

[9] *H. Weber*, Diplomarbeit, Universität München 1972.

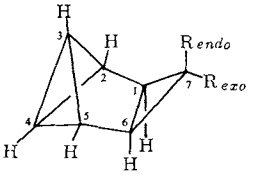
[10] *Note added in proof* (March 4, 1974): The kinetics of the reaction of *anti*-9-methyl-*cis*-bicyclo[6.1.0]nona-2,4,6-triene with excess TCNE in CH_3CN at 31.3 °C leads to the same result as for *(1)*.

Novel Isomers of Cycloheptatriene: Tricyclo[4.1.0.0^{2,7}]hept-3-ene and Tetracyclo-[4.1.0.0^{2,4}.0^{3,5}]heptane

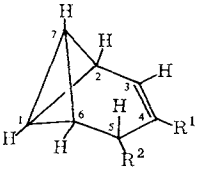
By *Manfred Christl* and *Gisela Brüntrup*[*]

We recently reported the conversion of benzvalene into *(1a)* by reaction with dibromocarbene[1]. In the present communication it is shown how previously unknown, highly-strained hydrocarbons are accessible *via* their halogen derivatives by the use of this reaction. The isomerizations of the compounds prepared throw new light on the reactivity of the bicyclobutane system.

Reaction of benzvalene with methyl trichloroacetate and sodium methoxide leads to formation of the dichloro derivative *(1b)* (colorless liquid, b.p. 77—79 °C/13 torr) in 84% yield[2]. On heating *(1a)* and *(1b)* rearrange into the allyl compounds *(2a)* (m.p. 38.5—39.5 °C)[2b] and *(2b)* (b.p. 91—93 °C/13 torr)[2b] respectively. When carried out in carbon tetrachloride solution at 80 °C, rearrangement of *(1a)* proceeds quantitatively within 15 h, whereas in the case of *(1b)* the solution must be heated for five days at 100 °C. When *(2a)* is heated for 75 h at 115 °C in tetrachloroethylene, drastic bond rearrangement takes place with formation of 3-bromobenzyl bromide.



(1a), R = Br
(1b), R = Cl
(1c), R = H

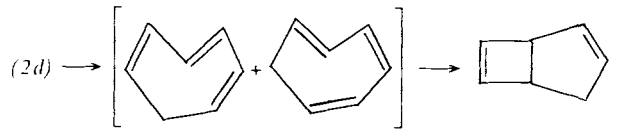


(2a), $R^1 = R^2$ = Br
(2b), $R^1 = R^2$ = Cl
(2c), R^1 = Br, R^2 = H
(2d), $R^1 = R^2$ = H

Reduction of *(2a)* with $LiAlH_4$ affords the monobromo derivative *(2c)* (colorless liquid, b.p. 60 °C/11 torr, yield 81%)[2b], which on reaction with sodium in liquid ammonia is converted into the unsubstituted tricyclo[4.1.0.0^{2,7}]hept-3-ene *(2d)* (colorless liquid, b.p. 111—112 °C, yield 70%)[2b]. Diagnostic for the bicyclobutane systems in *(2c)* and *(2a)* are the characteristic values of the ^{13}C—H coupling constants of the bridgehead protons 1-H and 7-H. Their values of 212 and 209 Hz, respectively, are somewhat larger than in tricyclo[4.1.0.0^{2,7}]-heptane (200 Hz)[3]. Reduction of *(1b)* with sodium in liquid ammonia affords tetracyclo[4.1.0.0^{2,4}.0^{3,5}]heptane *(1c)* (colorless liquid, b.p. 104 °C) in 70% yield. Its NMR spectrum shows an interesting long-range coupling of 2.4 Hz between the distant 4-H and 7-H_{exo}, as revealed by decoupling of 4-H.

On heating in C_2Cl_4 solution at 150 °C, *(2d)* is converted (reaction halflife *ca.* 1.5 h) into bicyclo[3.2.0]hepta-2,6-diene *(4)*, the photoisomer of cycloheptatriene, which could be identified by its NMR spectrum[4]. We assume, by analogy with the thermolysis of tricyclo[4.1.0.0^{2,7}]heptane[5], that a synchronous $[_\sigma 2_s + _\sigma 2_a]$ reaction takes place initially with formation of *cis-trans-cis*- and/or *trans-cis-cis*-cycloheptatriene [*(3a)* and *(3b)* resp.], which then lose their high strain by conrotatory "tying-off" of the cyclobutene ring with formation of *(4)*.

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(2d) (3a) (3b) (4)

On completion of reaction the product contains, in addition to *(4)*, about 10% of cycloheptatriene, which is formed in a side reaction, since ring expansion of *(4)* proceeds only very slowly at 150°C. A hydrogen shift onto the carbon atom projecting into the ring of the intermediate *(3)* might take place as a branch reaction; this would constitute a direct route to the cycloheptatriene. Treatment of *(2a)* with silver tetrafluoroborate at room temperature yields pure cycloheptatriene.

Despite its strain energy of approximately 100 kcal/mol *(1c)* is thermally pretty stable. On heating in tetrachloroethylene at 150°C it rearranges with a reaction halflife of *ca.* 5 h into cycloheptatriene.

If a synchronous reaction were to take place here, as in the case of *(2d)*, one could expect formation of *(4)* in a process involving electrocyclic ring expansion of the *cis-trans*-norcaradiene intermediate to the *cis-trans-cis*-cycloheptatriene *(3a)*. Either *(3a)* is converted into cycloheptatriene *via* a rapid 1,5 H-shift or diradical processes are involved[5].

The $AgBF_4$-catalyzed rearrangement of *(1c)* in cycloheptatriene proceeds explosively at room temperature. At −70°C, however, the reaction rate is already so slow that there is no hope of being able to observe the possible intermediate norcaradiene directly at considerably lower temperatures before its valence isomerization.

Received: December 3, 1973 [Z 973 IE]
German version: Angew. Chem. *86*, 197 (1974)

[1] *M. Christl*, Angew. Chem. *85*, 666 (1973); Angew. Chem. internat. Edit. *12*, 660 (1973). The yield of *(1a)* is now up to 57%.

[2] a) All the new compounds gave correct C,H analyses and mass spectra values; b) the NMR spectra are in accord with given structures.

[3] *G. L. Closs* and *L. E. Closs*, J. Amer. Chem. Soc. *85*, 2022 (1963).

[4] *W. G. Dauben* and *R. L. Cargill*, Tetrahedron *12*, 186 (1961).

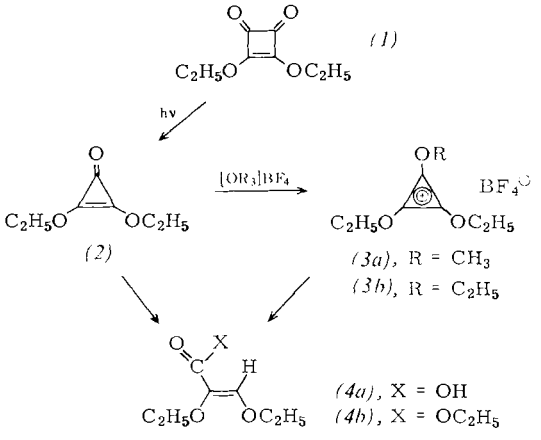
[5] *K. B. Wiberg* and *G. Szeimies*, Tetrahedron Lett. *1968*, 1235.

Trialkoxycyclopropenylium Ions[**]

By *Eckehard V. Dehmlow*[*]

Although alkoxy groups are among the best stabilizers of carbenium ions, trialkoxycyclopropenylium ions have so far not been accessible. We were recently able to show that diethyl triangulate [diethoxycyclopropenone *(2)*] is formed during the pyrolysis of diethyl squarate *(1)* in anhydrous ether[1]. Reaction of *(2)* with trimethyloxonium or triethyloxonium fluoroborate in methylene chloride and subsequent treatment of the concentrated reaction product after a few hours with anhydrous ether affords the crystalline salts *(3a)* (m.p. 87°C[***]) and *(3b)* (m.p. 113°C[***]).

The structure of *(3a)* and *(3b)* follows from elemental analysis and spectral data: while the NMR spectrum of *(3b)* in $CDCl_3$ shows only a singlet and a triplet (2:3) at $\tau = 5.28$ and 8.48 respectively, that of *(3a)* contains a quartet at $\tau = 5.24$, a singlet at 5.55, and a triplet at 8.43 (4:3:6). Thus the symmetrical structure of the ions is verified. The shifts of the signals compared to those of *(2)* [$\tau = 5.71$ (q), 8.57 (t)] and the



increased difference of about 0.34 ppm of the chemical shifts of the methylene and methyl signals indicate that the positive charge is considerably delocalized to the environs of the oxygen atoms.

The mass spectrum of *(3a)* reveals three primary fragmentations from the molecular ion 157: loss of CH_2O, loss of CH_3CHO (base peak), and loss of C_2 to the stable trialkoxycarbenium ion.

Compounds *(3a)* and *(3b)*, like *(2)*, are hygroscopic. However, while *(2)* is opened relatively slowly to *(4a)* and *(4b)* on reaction with water or ethanol, treatment of *(3b)* with water leads to immediate conversion into *(4b)*. This finding is somewhat surprising, since triaminocyclopropenylium salts can be recrystallized from water[2]. Their hydrolysis with alkali affords diaminocyclopropenones as well as ring-opening products[3].

The recently described tris(alkylthio)cyclopropenylium salts[4, 5] react similarly with water yielding dialkylthiocyclopropenones[5].

All attempts to transform *(1)* into the tetraalkoxycyclobutenediylium ion by reaction with an excess of Meerwein reagent have so far failed. *(1)* was still IR spectroscopically detectable even after prolonged reaction time.

Received: December 27, 1973 [Z 974 IE]
German version: Angew. Chem. *86*, 203 (1974)

[***] In a sealed tube.

[1] *E. V. Dehmlow*, Tetrahedron Lett. *1972*, 1271.

[2] *Z. Yoshida* and *Y. Tawara*, J. Amer. Chem. Soc. *93*, 2573 (1971).

[3] *Z. Yoshida, H. Konishi, Y. Tawara, K. Nishikawa*, and *H. Ogishi*, Tetrahedron Lett. *1973*, 2619.

[4] *R. Gompper* and *U. Jersak*, Tetrahedron Lett. *1973*, 3409.

[5] *Z. Yoshida, S. Miki*, and *S. Yoneda*, Tetrahedron Lett. *1973*, 4731.

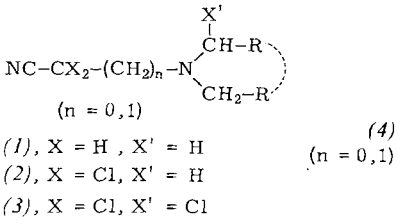
[*] Prof. Dr. E. V. Dehmlow
Organisch-Chemisches Institut der Technischen Universität
1 Berlin 12, Strasse des 17. Juni Nr. 135 (Germany)

[**] This work was sponsored by the Senator für Wirtschaft des Landes Berlin with financial support of ERP special funds; thanks are due to Frau *H. Klabuhn* for experimental assistance.

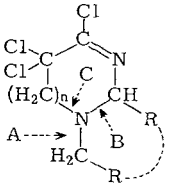
Highly Chlorinated Systems by Ring Closure Reactions

By *Gunther Beck* (lecturer), *Helmut Heitzer*, and *Hans Holtschmidt*[*]

Cyanomethylated and cyanoethylated secondary aliphatic amines *(1)* are converted by chlorination at 20—50 °C *via* isolable dichloro derivatives *(2)* into highly reactive non-isolable α-chloroalkylamines *(3)*, which spontaneously cyclize into five- and six-membered ring compounds *(4)* that are very sensitive to hydrolysis.



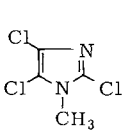
(1), X = H, X' = H
(2), X = Cl, X' = H
(3), X = Cl, X' = Cl



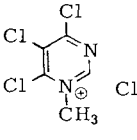
(4) (n = 0,1)

Further chlorination of compounds *(4)* at 50—130 °C affords stable imidazoles [*e.g. (5)* from dimethylaminoacetonitrile], 1-alkylpyrimidinium chlorides [*e.g. (6)* from 3-dimethylaminopropionitrile], or conjugated bicycles [*e.g. (7)* from 3-pyrrolidinopropionitrile].

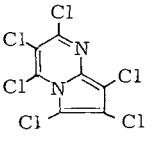
Still further chlorination between 100 and 200 °C leads to cleavage of *one* of the three N—C bonds marked A, B, and C in *(4)* (special case of "dealkylating high-temperature chlorination" of amines). Obviously the N—C bonds that are cleaved are those which lead to formation of the thermodynamically most stable end products.



(5)

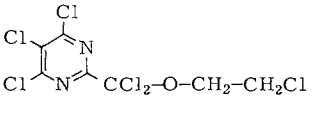


(6)

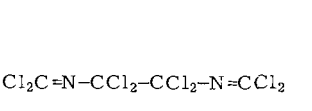


(7)

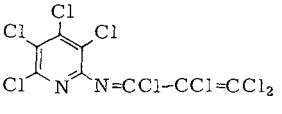
Cleavage at "A" usually occurs when $n = 1$, and affords pyrimidines, *e.g.* 4,5,6-trichloropyrimidine [from *(6)*] or *(8)* (from 3-morpholinopropionitrile). When $n = 0$, cleavage occurs at "B" and leads to perchlorodiazaalkadienes, *e.g. (9)* [from *(5)*]. The one case of cleavage at "C" observed so far occurred with bicyclic intermediate *(4)* from 3-piperidinopropionitrile: the 2-aminopyridine derivative *(10)* is the major product obtained.



(8)



(9)



(10)

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Lecture at München, November 6, 1973 [VB 376 IE]
German version: Angew. Chem. *86*, 134 (1974)

ABSTRACTS

Reviews

Abstracts of selected progress reports and review articles

The chalones are the subject of a review by *J. C. Houck* and *H. Hennings*. These compounds are cell specific, but not species specific mitotic inhibitors, which have been detected in mammals. Chalones from epidermis, melanocytes, fibroblasts, and lymphocytes are discussed. These involve proteins or glycoproteins, whose molecular weights differ very widely from one another. The article concludes with a discussion of the experimental difficulties and sources of error in the measurement of mitosis. [Chalones. Specific Endogenous Mitotic Inhibitors. FEBS Lett. *32*, 1—8 (1973); 50 references]
[Rd 680 IE—R]

The role of soluble protein factors in the translational control of protein synthesis in eukaryotic cells is the subject of a review by *V. M. Pain* and *M. J. Clemens*. As the slowest step, chain initiation is assumed to be the most important starting point of the regulating initiation factors. Under certain conditions the elongation or the loading of the t-RNA can be the site of regulation. Also included among the soluble factors are ribonucleases and their inhibitors which may likewise have a controlling function. [The Role of Soluble Protein Factors in the Translational Control of Protein Synthesis in Eukaryotic Cells. FEBS Lett. *32*, 205—212; 160 references]
[Rd 681 IE—R]

The reactivity and stability of arenediazonium ions constitute the subject matter of a report by *H. Zollinger*. After classifying the reactions of these ions the author goes on to consider nucleophilic reactions at N_β and at C-1 and the homolytic cleavage of the C-1—N_2 bond. It remains to be established

whether there is a common intermediate in homolytic and heterolytic decomposition of the diazonium ions. [Reactivity and Stability of Arenediazonium Ions. Accounts Chem. Res. *6*, 335—341 (1973); 65 references]

[Rd 688 IE—L]

Immunoglobulin receptors have been studied by *C. W. Pierce, R. Asofsky*, and *S. M. Solliday*. These authors have investigated the relation between the immunoglobulin class of the antigen receptors, which are located on the cell membrane of the precursors of antibody producers and that of the antibodies that are finally secreted by successors of these cells after stimulation by an antigen. The original precursor cells obviously contain receptors of the IgM class, independent of the type of antibody secreted later. A solitary immunization by an antigen leads to a temporary shift, longer immunization, on the other hand, to a permanent shift into the IgG class. [Immunoglobulin Receptors on B Lymphocytes: Shifts in Immunoglobulin Class During Immune Responses. Fed. Proc. *32*, 41—43 (1973); 21 references]

[Rd 682 IE—R]

The biological action of vitamin E and selenium is discussed by *A. T. Diplock* and *J. A. Lucy* on the basis of experiments on rat liver. Vitamin E evidently hinders the oxidation of selenide-containing non-heme iron proteins of the mitochondria and endoplasmic reticulum, which are responsible for detoxification processes. With the aid of molecular models it can be shown that vitamin E may form specific complexes within the cell membrane with highly unsaturated lipids that stem from the nutrient. Membranes free of vitamin E are very sensitive to phospholipases *in vivo* and towards dialuric acid and hydrogen peroxide *in vitro*; this could be due to their high permeability. [The Biochemical Modes of Action of Vitamin E and Selenium: a Hypothesis. FEBS Lett. *29*, 205—210 (1973); 37 references]

[Rd 677 IE—R]

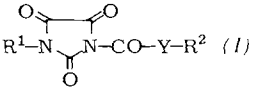
The carbohydrate components of surface glycoproteins of virus transformed cells are compared with those of normal cells by *L. Warren, J. P. Fuhrer*, and *C. A. Buck*. During growth transformed cells contain, in contrast to control cells, a sialic acid rich material of low elution volume in gel filtration whose formation depends on the presence of a sialyl transferase. In the case of temperature sensitive virus mutants the sialic acid rich material and the transferase were detected in large amounts only at lower temperatures at which the transformation also takes place. [Surface Glycoproteins of Cells before and after Transformation by Oncogenic Viruses. Fed. Proc. *32*, 80—85 (1973); 32 references]

[Rd 684 IE—R]

Patents

Abstracts of selected "Deutsche Offenlegungsschriften" (DOS), *i. e.* provisionally published specifications as filed with the German Patent Office

Polyimides of 1,4-benzoquinonetetracarboxylic acid with structural units *(1)* (R = aliphatic or aromatic residue) are obtained by reaction of 1,4-benzoquinonetetracarboxylic anhydride with diamines in solution at temperatures around 200 °C. These polyimides are stable up to 480 °C. They are partly soluble in organic solvents and readily soluble in a dithionite vat. They can be readily processed from the vat to form foils, films, fibers, and coatings, which are then converted back into the insoluble form by reoxidation with air and

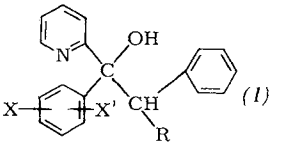


(1)

other oxidizing agents. From hydroquinonetetracarboxylic anhydride one obtains soluble polyimides, which also become insoluble on reoxidation. [DOS 2055211; Battelle-Institut e. V., Frankfurt a. M.]

[PR 132 IE—A]

The aggregation of blood platelets is inhibited by substituted quinazolines *(1)* or their salts. They differ in their biological action from anticoagulants such as heparin, and are suitable



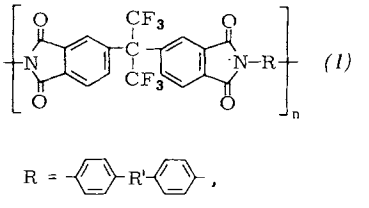
(1)

R^1 = H, alkyl (C_1—C_5), NH_2, alkylamino (C_1—C_4), alkoxy (C_1—C_4), CN, (halogen-substituted) phenyl, benzyl, phenethyl; R^2 = H, alkyl (C_1—C_5); R^3, R^4 = alkyl (C_1—C_5); $R^3 + R^4 = -CH_2-$

for the treatment of thromboembolic diseases. [DOS 2152521; Bristol-Myers Co., New York]

[PR 118 IE—N]

A laminar composite structure consisting of a reinforcing material and a polyimide *(1)* that can be blended in the melt is claimed. Synthetic organic fibers and materials such as asbestos, mica, graphite, and polytetrafluoroethylene are suit-



(1)

R = phenylene, *m*-phenylene, 1,5-naphthylene;
R' = —O—, —S—, —O—R''—O—; R'' = divalent aromatic residue

able for use as reinforcing materials. The type of structure described is suitable for high-temperature applications, *e. g.* for building panels. [DOS 2223819; E. I. du Pont de Nemours and Co., Wilmington]

[PR 119 IE—A]

Elastomeric olefin copolymers of ethylene and/or α-olefins and possibly dienes are obtained in high yields in liquid media at high monomer concentrations (at least 50 wt.%) and in the presence of a highly active catalyst system. The catalyst system is obtained by mixing a hydride or an organometallic compound of metals of groups I, II, and III of the periodic system [$Al(C_2H_5)_3$, $Al(iC_4H_9)_3$, $Al(C_2H_5)_2H$, $Al(iC_4H_9)_2H$ and $Al(C_2H_5)_2Cl$ are particularly suitable] with the product of the reaction of titanium or vanadium compounds with anhydrous Mg, Mn, In, or Ca halides. With the catalyst system described, it is possible to adjust the molecular weight of the copolymers or terpolymers to low and very low values with the aid of hydrogen or other chain-transfer agents without

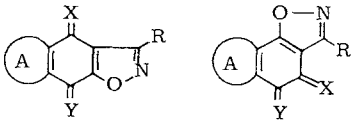
appreciable deterioration of the activity of the catalyst. [DOS 2150437; Montecatini Edison S.p.A., Milan]

[PR 134 IE—A]

Diethyl ketone can be prepared by decarboxylative dehydration of propionic acid in the presence of 0.25—1 mole of steam per mole of propionic acid on a catalyst containing thorium oxide at 350—400 °C in yields of 98—99.4%. The life of the catalyst is almost unlimited; practically no soot is deposited on the catalyst even when reactors made from high-grade steel containing nickel are used. [DOS 2111722; Badische Anilin- & Soda-Fabrik AG, Ludwigshafen]

[PR 149 IE—J]

Quinone derivatives *(1)* **and** *(2)* regulate the growth of plants and stimulate parthenocarpy. They also have a herbicidal and algicidal action. When used in concentrations of about 10 to 80 g/are they are found to be inactive against gramineae,



(1) *(2)*

R = halogen, lower alkyl, phenyl, pyridyl
A = (substituted) condensed benzene or pyridine ring
X, Y = —O—
X + Y = —O—CR=N—O—

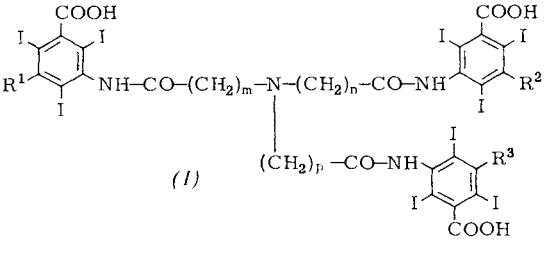
so that they can be used as selective herbicides or algicides. Their most important application, however, is probably in the production of seedless fruits, *e.g.* tomatoes, cucumbers, melons, *etc.* [DOS 2215722; Shionogi & Co. Ltd., Osaka]

[PR 143 IE—N]

The catalytic fluorination of vinyl chloride with hydrogen fluoride in the gas phase is carried out in the presence of a catalyst consisting of an (oxide) halide of trivalent, tetravalent, or pentavalent vanadium on active charcoal between 100 and 400 °C. The active charcoal should contain 1—40 wt.% of vanadium, and the catalyst should be treated with hydrogen fluoride before the reaction. The following fluorinated compounds are obtained: CHF_2—CH_3 (85—91%), $CHClF$—CH_3 (3—11%), and CHF=CH_2 (1—11%). [DOS 2215019; Solvay & Cie, Brussels]

[PR 153 IE—J]

Iodinated *N*-acyl derivatives of aromatic amino acids *(1)*, because of their low toxicity, high water-solubility, and low tonus (osmotic activity), are suitable for use as X-ray contrast media, particularly for vasographic work. They can be pre-



(1)

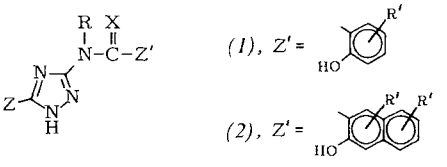
pared by reaction of 2 moles of a 3-(ω-haloacylamino)-2,4,6-triiodobenzoic acid with 1 mole of a 3-(ω-aminoacylamino)-2,4,6-triiodobenzoic acid. [DOS 2132614; Mallinckrodt Chemical Works, St. Louis]

[PR 154 IE—K]

Self-extinguishing fiber-reinforced polyolefin compositions consist of crystalline polypropylene or copolymers of propylene with up to 25% of other olefins, 10 to 50% of glass fibers, 4 to 45% of at least one commonly used flame-inhibiting organic halogen compound, 2 to 23% of antimony oxide, and 0.5 to 3% of a polypropylene or copolymer thereof modified with maleic anhydride. Examples of organic halogen compounds are chlorinated paraffins and chlorinated cyclic compounds, and preferably the 2:1 addition product of hexachlorocyclopentadiene with cyclooctadiene. In addition to their self-extinguishing properties, the polymers modified in this way exhibit an improved tensile strength. [DOS 2059022; Farbwerke Hoechst AG, Frankfurt/Main-Höchst]

[PR 164 IE—A]

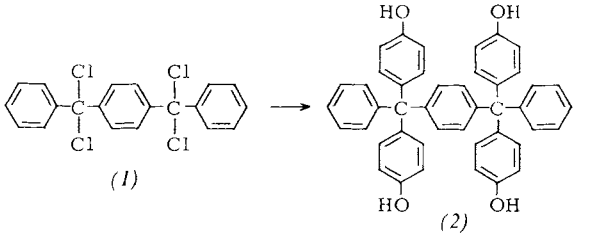
1,4-Bis(4,4'-dihydroxytriphenylmethyl)benzene *(2)* is prepared by reaction of 1,4-bis(α,α-dichlorobenzyl)benzene *(1)* with phenol; *(1)* can be obtained by chlorination of 1,4-dibenzylbenzene or of 1,4-dibenzoylbenzene by known methods. *(2)* can be used for the production of branched polycarbonates whose melts exhibit increased creep strength and which possess



improved non-Newtonian flow behavior and increased thermal stability. The new tetraphenol can also be used for the production of other plastics, *e.g.* of epoxy resins or phenol-formaldehyde resins. [DOS 2113347; Bayer AG, Leverkusen]

[PR 170 IE—U]

***N*-Triazolylsalicylamides** *(1)* **and *N*-triazolylbenzosalicylamides** *(2)* [R = H or alkyl (C_{1-4}); Z = H, alkyl (C_{1-18}), aryl, or alkylaryl (C_{0-18}), alkylenealkoxy or alkylenearyloxy (C_{2-18}), heterocycles (C_{4-5}) with one or two N atoms; X = O or S; R' = H, OH, SH, S-alkyl, S-alkenyl] are added to olefin



(1) *(2)*

polymerization products, *e.g.* polypropylene, to improve their resistance to oxidation. In the presence of the triazolylamides *(1)* and *(2)*, the usual catalytic effect of heavy metals on the degree of decomposition of the polyolefin is not observed. [DOS 2164234; S. A. Argus Chemical N. V., Brussels]

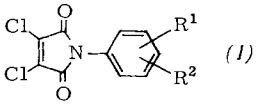
[PR 171 IE—E]

Polyoxazolidones with terminal NCO groups are obtained by reaction of organic polyisocyanates with polyepoxides at 100—150 °C in the presence of a Friedel-Crafts catalyst, *e.g.*

methylenedi(phenyl isocyanate), bisphenol A-epichlorohydrin adduct, $AlCl_3$, $FeCl_3$, or $ZnCl_2$. The epoxy/isocyanate equivalent ratio is 0.7—0.02. The reaction product is then trimerized to the isocyanurate preferably at 20 °C within 10 minutes with a catalyst such as tertiary amine, tertiary phosphane, or Friedel-Crafts catalysts. The products are suitable for the production of particularly flame-resistant foams, coatings, and molded articles. [DOS 2205731; Mitsubishi Chemical Ind. Ltd., Tokyo]

[PR 161 IE—A]

Dichloromaleimides *(1)* can be used for the control of plant and animal pests. They have good activity against bacteria

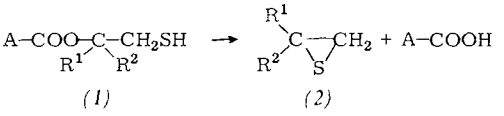


(1)

and fungi, and cause no side effects in warm-blooded animals. [DOS 2215787; Ciba Geigy AG, Basel]

[PR 142 IE—N]

Organic episulfides *(2)* can be prepared by decomposition of mercaptoalkyl esters *(1)* in the gas phase at 180—300 °C in the presence of Al_2O_3, which may contain 0.01—3 wt.% of Na_2O or up to 0.5 wt.% of Fe_2O_3 or up to 0.5 wt.%



(1) *(2)*

A = preferably CH_3
R^1, R^2 = H, alkyl, aryl, cycloalkyl

of SiO_2. The specific area of the catalyst is preferably between 10 and 250 m^2/g. [DOS 2222239; Société Nationale des Petroles d'Aquitaine, Courbevoie]

[PR 150 IE—J]

Polyamide imides are prepared by reaction of a) the reaction product of an acid containing three carboxyl groups with a) polyamine, b) an aliphatic unsaturated anhydride, and c) a polyisocyanate. Trimellitic anhydride is mentioned as a particularly suitable tricarboxylic acid. Suitable anhydrides include maleic, itaconic, and tetrahydrophthalic anhydrides as well as *endo-cis*-5-norbornene-2,3-dicarboxylic anhydride. Phenylenediamine, 4,4'-diaminodiphenylmethane, and 4,4'-diaminodiphenyl ether are used as polyamines. Examples of suitable polyisocyanates are 2,4-toluylene and diphenylmethane diisocyanates. The polymers are made into flexible films, which can withstand high temperatures *e.g.* in the field or electrical insulation. [DOS 2155678; General Electric Co., Schenectady]

[PR 133 IE—A]

BOOK REVIEWS

Methodicum Chimicum (Chemical Methods). Edited by *F. Korte*. Vol. 1: Analysis. Part 1: Purification, Wet Methods, Determination of Structures; Part 2: Trace Analysis, Biological Methods, Classes of Substance, Automation. Georg Thieme Verlag, Stuttgart, and Academic Press, New York—London 1973. 1st ed., x, 1263 pp., 413 figs., 14 schemes, 265 tables, bound DM 421.60 (individual volume price DM 496.—).

The aim of the Methodicum Chimicum, according to the Foreword, is to present "a short critical account of chemical methodology for science and practice". Accordingly, the main basis of classification in the present first volume, which deals with analytical methods in organic chemistry, is the *method*. The term "analysis" is given an extremely wide interpretation here. Thus in addition to separation methods (Chapter 2), methods for the chemical determination of classes of compound and functional groups (Chapter 3), spectroscopic and photometric methods (Chapter 5), fragmentation methods (Chapter 6), diffraction methods (Chapter 7), equilibrium and kinetic methods (Chapter 8), and special physical methods (Chapter 9), the book includes biochemical and biological methods (Chapter 13). The trace analysis of elements in organic materials (Chapter 10) is treated separately as a special problem, and the importance of chemical reactions for analytical purposes is also surveyed (derivative formation before the analysis, Chapter 4).

However, the division of the subject matter according to method is not rigorously followed. In two chapters (11 and 12), as a second aspect, the *application* of analytical methods to individual classes of substances is described for two important groups: for compounds of industrial interest (pesticides, drugs, food additives and impurities, organic compounds in water and effluents, petroleum products, fats, oils, and waxes, industrial gases) and for carbohydrates, proteins, and nucleic acids. Moreover, individual sections in the chapters on methods are predominantly problem-oriented: determination of configurations (3.8), determination of tautomer equilibria (8.3), detection and identification of electron donor-acceptor and δ complexes (9.6).

The scope of the volume is also very wide with regard to the information provided by the methods. In addition to the methods for the solution of the "normal" analytical problems (molecular weight determination, elementary analysis, detection, identification, quantitative determination, determination of the constitution and stereochemistry of molecules), it also deals with methods that lead predominantly to data on properties and charge distribution in molecules. A selection of methods for the investigation of macromolecules are also discussed. This diversity of the aspects considered and the wide scope make the list of contents seem rather motley. These factors also explain the large number of experts (103 are named) responsible for the 83 sections. In principle this presents a number of dangers. Repetitions have been avoided as far as possible, and are irritating only in the case of photoelectron spectroscopy (clear description of principle, measuring methods, theory, and applications in Section 5.10, described again as a recent development in 14.2.3). Disadvantages due to the separation of related groups of problems as a result of the chapter divisions chosen are also avoided in most cases by the use of cross references.

Cross references would have been useful between Section 5.1.9 (Electronic Spectroscopy), which deals with analytical applica-

tions, and Section 9.5, which deals, under the title "Nature, Multiplicity, and Properties of Excited States in Photochemical Reactions of Organic Molecules", mainly with the theory of the excitation and deactivation of electrons; it would also have been preferable to bring together the parts on elementary analysis (Sections 3.1, 3.2, and 14.4).

In general, attention should be drawn to the clarity of the description, the often very pointed indication of the possibilities and limitations of the methods, and the extensive list of references to monographs and relevant publications. These make the book very valuable as a source of information. However, it is also natural, simply because of the diversity of the methods discussed and of the aspects involved, that the extent and nature of the descriptions will vary from section to section, so that the user cannot expect to obtain the same kind of information from each contribution. A number of articles, particularly those on separation methods, methods of chemical analysis, trace analyses, and the analysis of special classes of substances, provide instructions for practical work, either directly or indirectly *via* literature references; in this respect, a comprehensiveness such as one might expect of a lexicon is found *e.g.* for the analysis of pesticides (11.1). Extensive tables are also given in many of the descriptions of physical methods to demonstrate their usefulness as aids, and special mention should be made of the description of IR spectroscopy (5.2), which is quite adequate for routine analyses. As far as other methods are concerned, the information for the user consists of a more or less comprehensive description of their principles, the principles of the equipment and/or measuring technique, and (usually with the aid of examples) the possible applications.

Though such a compilation of methods will undoubtedly be used mainly as a reference work for special problems, it is nevertheless gratifying that an attempt is made in the first volume of the "Methodicum Chimicum" to include even subsidiary aspects of analysis. This is outstandingly achieved in the chapters "Principles for the Assessment of Analytical Methods" (1) and "Aspects of the Choice of Suitable Separation Methods" (2.12); it is a pity that the similarly intended sections on "Use of Combined Instrumental Methods" (14.1) and "Trends in the Development of Instrumental Analysis" (14.2) are too short in comparison with these.

The richness of content of the volume and the variety of aspects discussed will guarantee it the wide range of users that it is intended to serve; though it is expensive, it will certainly be valuable in the handling of various problems.

Günter Kresze [NB 186 IE]

Mechanism—An Introduction to the Study of Organic Reactions. Oxford Chemistry Series. By *R. A. Jackson*. Clarendon Press, Oxford 1972, 1st ed., xiii, 136 pp., numerous figures, bound £ 1.10.

How can one determine, and in the ideal case prove, the mechanism of a reaction? The present book attempts to deal, at the second-year undergraduate level, with the criteria that are necessary for a study of reaction mechanisms: analysis of the reaction products, kinetic studies, reactive intermediates, stereochemical studies, "other arguments" (Hammett equation, solvent effects, Hammond postulate). Each chapter ends with a series of questions, and hints on the solution of the problems are given, together with the answers, at the end of the book. A short bibliography and the brief subject index complete the book. The problems are presented very clearly and skillfully with the aid of interesting examples. Anyone who has mastered the subject will enjoy reading the book. The student who is new to the material will sometimes have to consult a textbook as he works through the book, since some prior knowledge is presumed even with regard to the subject matter. The "Conclusions" at the end of each chapter provide the student with an additional opportunity to check that he has understood the essentials.

On the negative side, whereas there are only a few printing errors, the examples of cycloadditions in the chapter on stereochemistry are not very good, and the Woodward-Hoffmann rules should not be excluded at this level. In a new edition of the book, the literature references should always appear with the examples themselves in the individual chapters. Some of the reviews cited are too advanced for the readers at whom the book is aimed; lighter alternatives are available in these cases.

On the whole this book can be recommended to interested students preparing for final examinations. The price is also within the reach of students—a good example to some German publishers producing literature for students.

Jürgen Sauer [NB 190 IE]

Laser-Grundlagen und Anwendungen (Laser Principles and Applications). By *H. Weber* and *G. Herziger*. Physik-Verlag, Weinheim 1972. 1st ed., xi, 252 pp., 185 figures, 26 tables, bound DM 78.—.

The growing importance of laser applications in research and industrial production justifies a general account of the properties of laser light sources for readers with no prior knowledge of quantum mechanics. The book surprises the reader by its unconventional presentation and illustration, which enable one to take in even complicated laser effects at a glance. This presentation is no doubt excellently suited to the rapid instruction of the type of reader for whom the book is primarily intended, *i.e.* technologists and engineers. However, the specialist is more likely to be irritated by the many inconsistencies (which can surely be weeded out from the next edition) than to find pleasure in the unusual approach to quantum phenomena with the aid of analogy models.

Starting with a relatively broadly conceived introductory chapter on the spectral properties of classical radiation sources and optical resonators, the book deals with the following topics: laser oscillators, short light pulses, nonlinear optics, laser applications, and special optical elements of laser physics. Numerous comparisons from mechanics, hydromechanics, and electrotechnology are given as introductions. A useful addition to the relationships derived in this way would have been a simple mathematical description to enable the practical worker to estimate the feasibility of a laser project. Thus the section on dye lasers, deals at some length with triplet effects, but ignores the obvious derivation of the required pump rise times or a calculation of the inversion at the laser threshold, taking into account the connection mentioned in the text between fluorescence and reabsorption.

The book is very suitable for use as an easily understandable introduction to the physics of the laser. It can be recommended in particular to readers who wish to gain a quick general picture before tackling the specialist literature on their proposed application.

Gerd Marowsky [NB 181 IE]

Surface and Defect Properties of Solids, Vol. 1. Specialist Periodical Reports. The Chemical Society, London 1972. 1st ed., viii, 264 pp., numerous figures, bound £ 6.00.

In the nine chapters of this volume of "Specialist Periodical Reports", eleven authors present a survey of important results from the chemistry of solids published between January 1970

and April 1971. The earlier work connected with these results is naturally also discussed.

The first four chapters deal with the influence of one-dimensional and two-dimensional lattice defects on the structure and behaviour of solids. Ordered nonstoichiometric phases are described in "Shear Structures and Nonstoicheiometry". The shear structures can be observed directly by a high-resolution electron microscope phase contrast method, which is described in the next chapter. This method is particularly suitable for layer structures; in this way one can obtain a picture of the individual carbon layers in graphite and paracrystalline carbons, but investigations on polymers and macromolecules, *e.g.* DNA, are also reported. It is shown in two further chapters that dislocations are decisive for the occurrence of solid-state reactions even in organic chemistry, *e.g.* in polymerizations in molecular crystals. Five chapters deal with investigations on the surfaces of solids and their reactivity. As a result of recent progress on the equipment side, the methods of electronic spectroscopy are particularly suitable for the detection of foreign atoms in surfaces and their bonding. Photoemission, Auger spectroscopy, ESCA, and a few other methods are described in two chapters. Progress has also been made in the IR spectroscopy of molecules adsorbed on metals. Two further chapters deal with isotope exchange between gas molecules adsorbed on metals and some aspects of the selective action of metal catalysts.

This is the start of an attempt to forge a path through the jungle of wildly proliferating literature by means of handy reviews published at regular intervals, which is to be welcomed if it is kept up. The book will be of use to all workers and institutes concerned with surface and solid-state chemistry, though some of the authors almost exclusively cite English-language literature.

Hanns-Peter Boehm [NB 189 IE]

Air Pollution. Part A: Analysis. By *J. O. Ledbetter*. Marcel Dekker Inc., New York 1972. 1st ed., xii, 424 pp., numerous figures and tables, bound $ 11.75.

The concept of air pollution has not only been a focus of public interest for some time, but is now also attracting the interest of scientists, particularly of engineers, chemists, and analysts. The present work is capable of providing a conceptually and technically sound basis for the scientific treatment of air analysis problems. It should be emphasized that the author has not yielded to the temptation simply to give a collection of procedures under the sub-title "Analysis". On the contrary, he has managed to present all the facts relevant to the assessment of the analytical problem and to the evaluation of the analytical results in a succinct, precise, and impressive manner. In the first chapter, which deals with the background of the problem, the reader is acquainted with the essential basic facts, definitions, and units of measurement. The author then considers the sources of air pollution, and takes this opportunity to survey the principal components of air pollution.

Another chapter is devoted to the physical and chemical processes that take place in the atmosphere and that control the distribution, the dilution, the deposition, and the reaction of polluting substances in the atmosphere. This is followed by a very detailed description of the mathematical and statistical methods used in the design of measuring plans and in the interpretation of the sets of results obtained.

After a brief excursion into the physical chemistry of gases and the physics and chemistry of aerosols, four chapters are devoted to the actual analytical technique. The first deals with the design of measuring plans, presents a survey of the technical equipment necessary for sampling, and finally raises a number of practical points that must be noted in connection with air sampling. The chapter on the actual measuring technique begins with a description of the main characteristics of analytical methods, *e.g.* detection limits, reproducibility, and cross-sensitivity, then touches briefly on the procedures for the presentation of experimental results, and finally gives a very succinct review of the physical and chemical principles of the measuring procedures, including spectrochemical methods, chromatographic procedures, classical wet methods of analysis, and the methods of electroanalysis. The principles of the evaluation of smells, noises, and radioactive radiation are also discussed.

In two further chapters the author first goes into details of the measurement of aerosols, particularly with regard to the determination of particle sizes and their distribution, and then deals with a series of specific procedures.

The work ends with a chapter on the effects resulting from air pollution. The book is very readable and is provided with instructive diagrams; each chapter ends with a number of examples for practice and with references, which are unfortunately almost entirely confined to the Anglo-Saxon literature. German readers may be slightly irritated by the fact that the selection of examples, procedures, and equipment described in detail is essentially determined by the conditions prevailing in the United States. Nevertheless, it is to be hoped that this handy book will find a wide circulation among specialists and students.

Heinz Hartkamp [NB 187 IE]

Glycoproteins. Their Composition, Structure and Function. BBA Library, Vol. 5, Part A and B. Edited by *A. Gottschalk*. Elsevier Publishing Company, Amsterdam—London—New York 1972. 2nd ed., xxxviii, 1377 pp., 153 figs., 200 tables, bound, together $ 125.—.

Glycoproteins are found in bacterial cell walls and in plant hemagglutinins, and play a very specific role as components of animal tissue, *e.g.* in the proteins of serum and of eggs, in a number of enzymes, in collagen and fibrinogen, in thyroglobulin and the gonadotropic hormones, in the mucins of the mucous membranes, the joints, the blood-group substances, *etc.* The agglutination and virus-binding reactions are due to the glycoproteins of the cell membranes. The relatively short carbohydrate chains of these conjugated proteins contain eight to ten saccharide residues, and a special characteristic is that these include *N*-acetylamino sugars and sialic acid. In all these cases the characteristic properties can be destroyed by neuraminidase. The protein component is joined to the carbohydrate component *via* the amide group of asparagine or *via* the hydroxyl group of the hydroxy amino acids.

The then known physical, chemical, and analytical properties of the glycoproteins had been described in the first edition of this work[1]. The new edition, appearing six years later, indicates already by its size how much has been discovered in the meantime. A comparison of the contents shows that the emphasis is also beginning to shift from "static" descriptions to the function and biogenesis of the glycoproteins.

The first part presents a detailed and critical discussion of the methods for the determination of purity, molecular parameters, and composition of the glycoproteins, *i.e.* amino acid and sequence analyses, determination of amide nitrogen, characterization and identification of the sugars by gas chromatography, structural analysis of the carbohydrate component by chemical and enzymatic methods, and the methods for the detection of the sugar-protein linkage. A particularly difficult problem is presented by the increasingly recognized

heterogeneity of the carbohydrate chains in these substances, which may be regarded as stages or parallel products of their biosynthesis. The analytical part is followed by a description of the occurrence of glycoproteins in the plant and animal kingdoms and of individual groups of glycoproteins as well as their isolation, structure, and biological properties. The astonishing diversity of structure and function that was referred to earlier becomes evident here; there are metal binders and anti-freezes, enzyme inhibitors and cell-differentiating agents, immunoglobulins and nerve membrane components.

The second part initially continues this description with the mucins, blood-group substances, collagen, and sulfated glycoproteins. This is followed by the carbohydrate-containing hormones, enzymes, and other functional proteins and the virus/cell interactions. An important part is devoted to the biosynthesis, metabolism, and turnover of amino sugars and glycoproteins. This part includes not only the individual synthesis and breakdown steps but also the description of the specific enzymes, *e.g.* neuraminidase, and the reactions catalyzed by them.

The individual articles are written by a number of well-known experts in their field, sometimes with the co-authorship of *A. Gottschalk*, who in any case has carefully edited and coordinated all the contributions to give a homogeneous appearance to the entire monumental work. By means of detailed references extending up to very recent literature, and by the inclusion of many details, numerous illustrative tables, and clear formula schemes and diagrams, all the material has been worked out and prepared in such a way that this second edition, even more than the first, has become a "handbook", not merely on grounds of size, but, in the best sense of the word, because of its content. From this work one can learn the research in this field has advanced and one can also find out about its historical development, in which the editor played such a great part. The production of the volumes corresponds to their price, which will unfortunately be within the reach only of libraries and very well-endowed institutes, though the work should be accessible to as many as possible of those who are interested. They will find it to offer comprehensive information, sound instruction, and a wealth of noteworthy critical suggestions.

L. Jaenicke [NB 188 IE]

[1] Cf. Angew. Chem. internat. Edit. *6*, 1009 (1967).

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal.

Organometallic Compounds. Methods of Synthesis, Physical Constants and Chemical Reactions. Edited by *M. Dub*. Vol. II: Compounds of Germanium, Tin and Lead. By *R. W. Weiss*. First Supplement Covering the Literature from 1965 to 1968. Springer Verlag, Berlin 1973. XXV, 1116 pp., bound DM 112.90.

Rodd's Chemistry of Carbon Compounds, 2. Edit. Edited by *M. F. Ansell*. Supplement to Vol. 1: Aliphatic Compounds. Teil C: Monocarbonyl Derivatives of Aliphatic Hydrocarbons; Teil D: Dihydric Alcohols. Elsevier Scientific Publishing Co., Amsterdam 1973. XIX, 464 pp., bound Dfl. 120.—

Organic Reactive Intermediates. Edited by *S. P. McManus*. Vol. 26 der Reihe "Organic Chemistry". Academic Press, New York 1973. X, 539 pp., bound $ 39.50.

Contents: Free Radicals; Carbenes; Nitrenes; Carbonium Ions; Carbanions; Radical Ions; Arynes.

Current Topics in Microbiology and Immunology, Vol. 40: Ergebnisse der Mikrobiologie und Immunitätsfoschung. Edited by *W. Arber et al.* Springer-Verlag, Berlin 1973. IV, 142 pp., bound DM 48.—.

Coordination Chemistry. Experimental Methods. By *K. Burger*. Butterworths, London 1973. 372 pp., bound £ 10.00.

Advances in Molten Salt Chemistry, Vol. 2. Edited by *J. Braunstein, G. Mamantov* and *G. P. Smith*. Plenum Press, New York 1973. XI, 259 pp., bound $ 23.00.

Contents: Physical Properties; Solubilities of Gases; Coordination Chemistry; Electroanalytical Chemistry.

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Analysis of Herbicides[**]

By Hans-Peter Thier[*]

Herbicides, like other pesticides, leave undesirable residues on the treated plants. To analyze them, the plant material is extracted and the herbicidal residues are separated from the bulk of the co-extractives of natural origin, about which too little is known. Quantitative determinations at the ppm level are best performed by gas chromatography with highly sensitive, specific detectors. In food control, where the history of the sample is unknown, the herbicide residues are identified and determined quantitatively together with the residues of other pesticides.

1. Introduction

In modern plant protection, numerous insecticides, acaricides, and fungicides are used to guard the growing plants and harvests against damage by insects, mites, or fungus diseases and thus to prevent threatened economic losses. A logical addition to this group of substances is the herbicides[1–4]. These are used to allow the use of more rational cultivation methods, in which harvest losses can be avoided and labor saved.

Herbicides in the broadest sense are any compounds that can influence the growth of higher plants. They intervene in various steps of the respiration, photosynthesis, or nucleic acid metabolism, and so inhibit the normal development of the plants[5–8].

The most drastic are the total herbicides, which are used to eliminate vegetation from paths, railway embankments, and ditches. They are also used in agriculture, *e.g.* to kill the tops of potato plants before harvesting by machine.

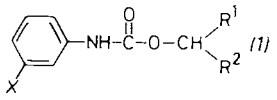
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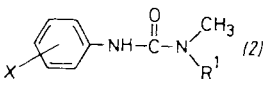
[**] Based on a plenary Lecture to the "Trace Analysis" Conference of the "Analytical Chemistry" Group of the German Chemical Society in Erlangen, April 2 to 5, 1973.

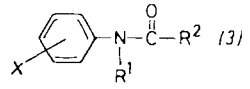
Most of the active substances are selective herbicides, which are used to combat weeds. Depending on the manner in which they act, they are used before sowing, before or after the cultivated plants emerge, or only during the later stages of their development. In addition to their use in agriculture, *e.g.* for cereal crops or sugar beet, they are being increasingly used in vegetable and fruit growing and in vine cultivation. In these areas they are displacing the traditional mechanical weeding, which is no longer sufficiently economical, and in many cases it is only through the use of such agents that machine harvesting is possible in large monocultures, *e.g.* for spinach.

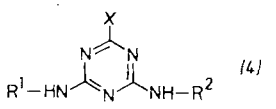
Finally, growth regulators are used to influence the cultivated plants themselves. Examples are the shortening and thickening of the stalks of cereals, the prevention of undesirable lateral branches in tobacco plants, and the thinning of fruit in fruit growing.

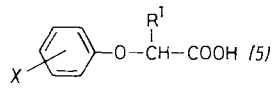
In recent years the herbicides have far surpassed the other pesticides in their economic importance. At the same time, new compounds are continuously being developed and officially adopted. Thus in 1969 the list of compounds permitted for use in pest control[9] in the German Federal Republic contained only 44 herbicides, whereas the number had increased to 65 in 1972. Table 1 shows a selection of these compounds, which are generally marketed in several formulations and under many trade names.


(1)


(2)


(3)


(4)


(5)

and the influence of its microflora[15] must also be taken into account. Since the active compound is known in analyses of this nature, the analyst's job amounts only to a quantitative determination; the detection sensitivity in plant material or soil samples should be as high as possible[16] ("Individual Methods", see Section 3).

In the crops that are consumed as food, the herbicide residues are generally far below the maximum permissible tolerance levels calculated on the basis of chronic toxicity tests on animals[1]. However, higher concentrations can occur in some cases, since excessive application, application at the wrong time, or unfavorable weather influences cannot be ruled out in agricultural practice.

Table 1. Structures of some common herbicides [9].

		X	R^1	R^2
Carbanilic esters (1)				
(1a),	Propham, PC	H	CH_3	CH_3
(1b),	Chlorpropham, CIPC	Cl	CH_3	CH_3
(1c),	Chlorbufam	Cl	CH_3	C≡CH
(1d),	Barban	Cl	H	CH_2—C≡C—CH_2Cl
N-Phenylureas (2)				
(2a),	Monuron	4-Cl	CH_3	
(2b),	Monolinuron	4-Cl	OCH_3	
(2c),	Diuron	3-Cl, 4-Cl	CH_3	
(2d),	Linuron	3-Cl, 4-Cl	OCH_3	
(2e),	Chlortoluron	3-Cl, 4-CH_3	CH_3	
(2f),	Buturon	4-Cl	$CH(CH_3)$—C≡CH	
Anilides (3)				
(3a),	Monalide	4-Cl	H	$C(CH_3)_2$—C_3H_7
(3b),	Pentanochlor	3-Cl, 4-CH_3	H	$CH(CH_3)$—C_3H_7
(3c),	Propachlor	H	$CH(CH_3)_2$	CH_2Cl
1,3,5-Triazines (4)				
(4a),	Simazine	Cl	C_2H_5	C_2H_5
(4b),	Atrazine	Cl	C_2H_5	$CH(CH_3)_2$
(4c),	Propazine	Cl	$CH(CH_3)_2$	$CH(CH_3)_2$
(4d),	Prometryne	SCH_3	$CH(CH_3)_2$	$CH(CH_3)_2$
Chlorophenoxycarboxylic acids (5)				
(5a),	2,4-D	2-Cl, 4-Cl	H	
(5b),	2,4,5-T	2-Cl, 4-Cl, 5-Cl	H	
(5c),	Dichlorprop, 2,4-DP	2-Cl, 4-Cl	CH_3	
(5d),	Mecoprop	2-CH_3, 4-Cl	CH_3	
(5e),	MCPA	2-CH_3, 4-Cl	H	

2. Objectives of Residue Analysis

If plant protection agents are not broken down quickly enough after use, the cultivated plants contain measurable residues after harvesting, and these may be absorbed into the human body on consumption of fruit, vegetables, or cereal products. The herbicides do not have such worrying properties as some insecticides, *e.g.* the high acute toxicity of numerous organophosphates or the pronounced persistence of some chlorinated hydrocarbons; nevertheless, any exposure of man to additional hazards is undesirable.

There are thus two main objectives in the analysis of herbicides, which differ in the questions raised and the analytical methods used.

The first objective is to learn about the behavior and the fate of a herbicide in nature. This will involve investigations on how quickly and by what route the compound is absorbed by the plant[10], in which parts of the plant it accumulates, at what rate and by what chemical reactions it is decomposed or metabolized[11, 12], and what external factors, such as climate or other ingredients of the formulation, influence this breakdown. The reactions that take place in the soil[13, 14]

The second objective of herbicide analysis is therefore the continuous control of agricultural commodities placed on the market. The history of the product in these cases is usually unknown, and the analyst consequently requires analytical methods that allow both the identification and the quantitative determination of any residues present. The scope of such a "screening analysis" and the detection sensitivity required will be decided by the tolerances established for food products under the country's regulations. In the German Federal Republic, for example, the residues of 50 herbicides in plant foodstuffs must not exceed levels between 0.01 and 1.0 ppm[17] (see Section 4).

3. Individual Methods

Every residue analysis comprises three steps: the extraction of the sample material, the clean-up of the crude extract to concentrate the herbicide and separate it from co-extracted matter and the final determination of the residue in the purified extract.

The main difference from other trace analyses of the same type is that in the case of plant material or soil samples, too little is known about the numerous natural constituents of the substrates. Consequently, these substances can only be separated by empirically developed methods, and difficulties may be expected as soon as a different sample material is to be analyzed. Special difficulties are usually encountered in the isolation of herbicides in the presence of low molecular weight, lipophilic, and volatile plant constituents such as essential oils and flavor substances that occur *e.g.* in onions, cabbage, or carrots.

3.1. Extraction and Clean-Up

The analysis is generally carried out on 50 to 100 g of plant material or soil sample. Most of the lipophilic herbicides are extracted from this material by homogenization with a low-boiling water-miscible solvent such as acetone, methanol, or acetonitrile. The crude extract, which also contains most of the water from the sample, is concentrated under vacuum and is subsequently partitioned between the remaining aqueous solution and petroleum ether, ether, methylene chloride, or chloroform.

In addition to the herbicide to be analyzed, other lipophilic material such as fats and waxes, flavor substances, and coloring agents also pass into the organic phase. Herbicides with free carboxy, phenolic hydroxy, or amino groups [*e.g. (5)*] can be very easily separated from this mixture by extraction with alkaline or acidic solutions, since they pass into the aqueous phase as salts. Carbanilic esters *(1)* or *N*-phenylureas *(2)* are often hydrolyzed to the anilines, which can be isolated by steam distillation.

In most cases, however, the extract must be further purified by adsorption chromatography. The preferred technique is separation on columns packed with alumina or the magnesium silicate Florisil®, from which the herbicide in question can be eluted with a solvent mixture of suitable polarity. Columns packed with silica gel, activated carbon, or magnesium oxide are less commonly used. This is also true of thin layer and thick layer chromatography, which are used only when a satisfactory separation cannot be achieved in any other way. The extract may occasionally be further purified by other methods, as in the analysis[18] of the three chlorotriazine derivatives *(4a)*, *(4b)*, and *(4c)* by chromatography on a column packed with $NaHSO_4 \cdot H_2O$ at -20 °C. A clean-up of this type is illustrated schematically in Figure 1.

A simpler clean-up can be used in the determination of the very water-soluble herbicides *(7a)*, *(7b)*, and *(8)*. Because of their strong absorption on organic material, these compounds can sometimes be extracted only in the presence of strong acids. They are separated from the aqueous extract on a strongly acidic ion exchanger[19], from which they are subsequently eluted with salt solutions.

In every clean-up step, part of the pesticide is inevitably lost, either through losses on evaporation of solvents or through irreversible adsorption on the surface of glassware or of adsorbents. Moreover, interfering substances may be introduced into the analysis by packaging material[20], solvents[21–23], reagents[24], filter paper[25], *etc.* In any clean-up procedure, therefore, it is necessary to determine first, in one's own laboratory, the percentage of recovery by fortifying untreated sample material with the pesticide at the level expected in the analysis. A recovery of 70% on addition of 0.1 ppm of a herbicide may be regarded as satisfactory, as long as the results are reproducible.

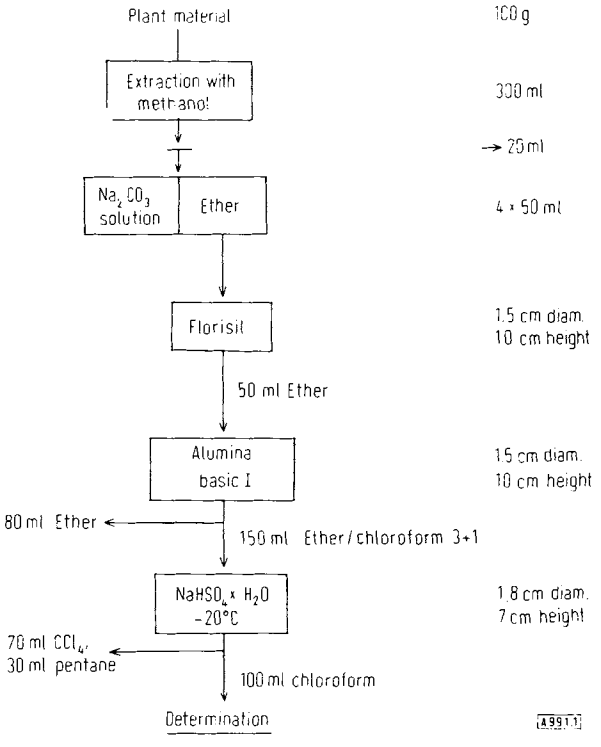


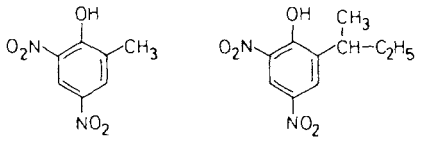
Fig. 1. Clean-up scheme for the analysis of the chlorotriazines *(4a)*, *(4b)*, and *(4c)* simplified after [18].

3.2. Determination

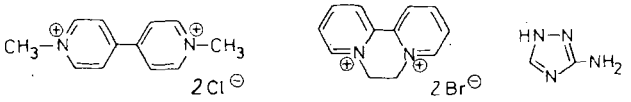
Even when the extracts have been thoroughly purified, they usually still contain a few milligrams of unwanted substances of unknown composition as well as microgram quantities of the herbicide to be determined. Methods such as IR spectrometry, mass spectrometry[26, 27], or polarography[28] can therefore only rarely be used, possibly in monitoring water, which has a very low content of organic matter. Measurements of biological activity[29], which would be very suitable because of their specificity, are generally too time-consuming for routine analyses.

On the other hand, there are many photometric methods, and colorimetric methods in particular[16, 30] not requiring large-scale apparatus. Thus dinitrophenols such as DNOC *(6a)* and dinoseb *(6b)* can be sensitively determined by means of the yellow color of the phenolate, while the dications of the bipyridine compounds[31] paraquat *(7a)* and diquat *(7b)* are reduced to colored radical-ions by sodium dithionite.

Herbicides with free aromatic amino groups, such as amitrole *(8)*[32], are diazotized and coupled with chromotropic acid or similar compounds to form an azo dye. Carbanilic esters *(1)*, *N*-phenylureas *(2)*, and other herbicides can also be determined in the same manner[16, 30] if they are hydrolyzed to the anilines during the clean-up or before the determinative step; *N*-(1-naphthyl)ethylenediamine is used as the coupling component in most cases. However, interference can be caused here by *o*-aminoacetophenone, which is thought to be formed from tryptophan on alkaline hydrolysis[33]. When high blanks



(6a) (6b)

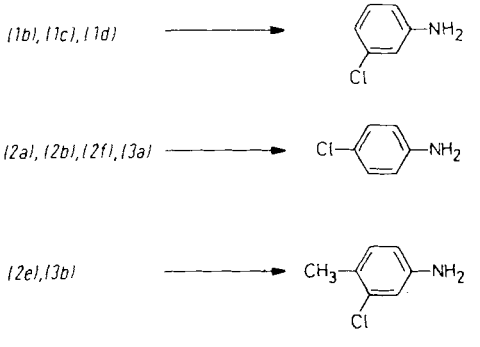


(7a) (7b) (8)

are obtained, therefore, the dye solution must be further purified by chromatography on a cellulose column.

If the herbicide does not offer any point of attack for a colorimetric determination, the problem can be overcome by direct UV measurement (*e.g.* in the case of α-naphthylacetic acid[34]) or by the preparation of suitable derivatives, *e.g.* by acid hydrolysis of the 2-chlorotriazines *(4a)*, *(4b)*, and *(4c)* to the 2-hydroxy compounds[1,8], whose cation has an absorption maximum at 240 nm. Fluorimetric determination is also possible in a few cases, *e.g.* for α-naphthylacetic acid[35] or β-naphthoxyacetic acid[36].

All optical measurements are sensitive (detection limit in most cases between 1 and 10 μg), but they are also very non-specific. In addition to accompanying natural substances from the sample material, the determination frequently also responds to the metabolites of the herbicide under investigation. Interference may also be caused by other pesticides that have the same functional groups or form a similar derivative (Scheme 1).



Scheme 1.

In a quantitative determination by chromatographic methods, on the other hand, one simultaneously obtains information about whether the value obtained does in fact refer to the compound to be analyzed. In thin layer chromatography, however, co-extractives can seriously alter the R_f values and hinder the quantitative estimation, which is usually based simply on a visual comparison of the spot size with a standard series. Methods of this type have been described *e.g.* for the determination of the triazine derivatives *(4a)*, *(4b)*, and *(4c)* in UV light[16,18] and for the carbanilic esters propham *(1a)* and chlorpropham *(1b)*, which are hydrolyzed by heating of the plate and treated with *p*-dimethylaminobenzaldehyde to form colored compounds[37].

During the past few years, gas chromatography has become one of the most important determinative methods for residue analysis[38,39,92]. This is due to the development of new, highly sensitive detectors[39-42], with which herbicides containing characteristic elements or functional groups can be selectively determined in the nanogram range. Because of this low detection limit, only a small aliquot of the extract is required for the analysis, with the result that the interference by co-extracted material is greatly reduced.

The separation is always performed on packed glass columns containing 0.5—15% of a liquid phase on a substantially inert support material. The columns have to be very carefully conditioned to avoid losses due to irreversible adsorption or decomposition.

In the microcoulometric detector[42-44], nitrogen compounds eluted from the separating column are reductively pyrolyzed with H_2 on a nickel catalyst; the resulting NH_3 is then neutralized in a titrating cell with coulometrically generated $H^{\oplus}$ ions. In the Coulson electrolytic conductivity detector[44-49,90], the compound is degraded in the same manner, but the NH_3 is then dissolved in a film of water and the conductance of the solution is monitored. After suitable modification, both detectors can also be used for the determination of herbicides containing Cl, Br, I, P, or S[39,50,51]. Alternatively, these elements can be detected with emission-spectrometric detectors, in which excitation is achieved in a flame or in a microwave plasma (flame photometric detector[52,53] and microwave emission detector[54-56]) and a strong spectral line of the element in question is quantitated.

The equipment required for the thermionic nitrogen detector (N-TID) is more simple[57-60]. In this case a crystal of Rb_2SO_4 or RbBr is positioned on or a few millimeters above the flame jet of the conventional flame ionization detector; the gas flow rates are adjusted to give a relatively cool reducing flame. The carbon signals are lowered by the hindered combustion, whereas compounds containing nitrogen (and phosphorus) increase the ionization current to a much greater degree than in the normal flame ionization detector. A selectivity of C : N = 1 : 3000 can be achieved with an optimum arrangement[61]. The detection limit is reported to be 1 pg of N/s; the linear range is about 10^4.

The signal area/g is proportional to the nitrogen equivalent in the compound to be determined. The N-TID is therefore particularly suitable for the analysis of the triazine herbicides *(4)*[28,62,63], which all contain five N atoms in the molecule. For the analysis of carbanilic esters *(1)* or *N*-phenylureas *(2)*, however, it can only be used in some special cases[64], since these compounds mostly decompose during the gas-chromatographic separation[65].

The electron capture detector (ECD)[42] has been the most widely used so far in residue analysis. In this device the carrier gas is first ionized by β rays from a ^3H or ^{63}Ni source to form positive ions and slow electrons; on application of a D.C. voltage (often pulsed), these are collected to produce a basic current. If other molecules pass through the detector, they capture some of these electrons and form negative ions, which later recombine with the positive ions of the carrier gas molecules. The loss of electrons is recorded as a decrease in the basic current. The relatively narrow linear response of the detector can be extended to a range of about 10^4 by a mode of operation in which the basic current is kept constant by continuously modulating the pulse frequency[66,67].

The specificity of the ECD is due to the difference in the electron affinities of organic molecules. The detector is particularly sensitive to compounds containing nitro groups or halogen atoms (I > Br > Cl > F). The size of the signal depends mainly upon the number of capturing species (Fig. 2), but is also affected by their position in the molecule and the type of bonding[68].

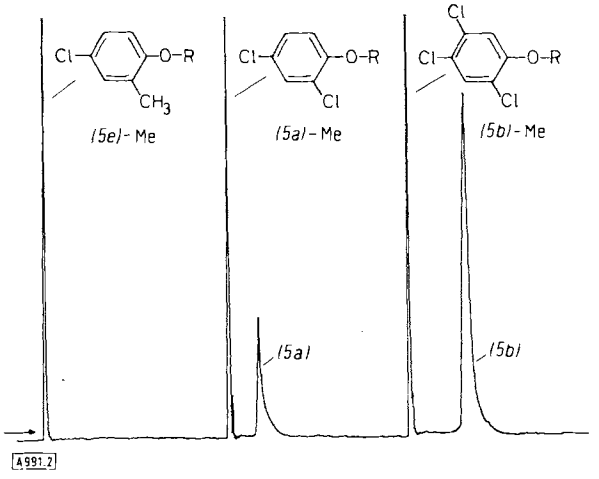
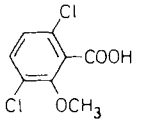


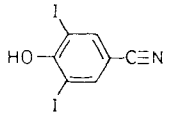
Fig. 2. Gas chromatogram of the methyl esters of the three chlorophenoxy carboxylic acids *(5e)*, *(5a)*, and *(5b)* (R = CH_2—$COOCH_3$) (1 ng in each case) with the electron capture detector (ECD). Operating conditions: 1 m 10% SE-30, 170 °C, 120 ml/min of Ar (5% CH_4), ECD (^{63}Ni).

In the analysis of herbicides, the ECD is employed primarily for the determination of the widely used chlorophenoxy carboxylic acids[69] such as 2,4-D *(5a)* and 2,4,5-T *(5b)*, the chlorobenzoic acids[70] such as dicamba *(9)*, and the halogenated[71] and nitrated[72] phenols such as ioxynil *(10)* and dinoseb *(6b)*. Before the gas chromatography, these compounds are all methylated with diazomethane[71,73], BF_3/methanol[74], or dimethyl sulfate[75], and they can be detected in quantities of 0.1–1 ng. A number of other herbicides, such as bromacil *(11)*[76] and trifluralin *(12)*, or diuron *(2c)*[91], can be determined directly.

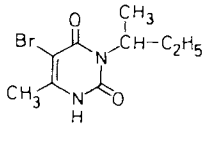
(9)



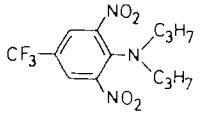
(10)



(11)



(12)



It can be seen from Figure 2 that herbicides containing only one chlorine atom are not detected by the ECD at the nanogram level. The detection sensitivity here can be improved in a range of about 10–100 by preparation of derivatives that contain additional electron-capturing groups.

For the *N*-phenylurea monuron *(2a)*, for example (Fig. 3), the 4-chloroaniline formed on hydrolysis may be allowed to react with 4-chloro-3,5-dinitro-α,α,α-trifluorotoluene[77], or it may be diazotized and converted by Sandmeyer reaction into 1-chloro-4-iodobenzene[78]; another possibility is bromination of *(2a)* with simultaneous hydrolysis to form 2,6-dibromo-4-chloroaniline[79].

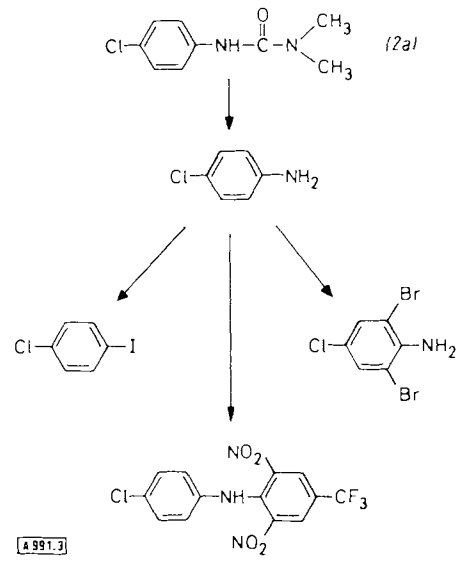


Fig. 3. Derivatives of monuron *(2a)* that are suitable for gas-chromatographic detection with the electron capture detector (ECD).

Misinterpretations are possible, however, since the same derivatives are also obtained from metabolites of monuron and from all other herbicides that yield 4-chloroaniline on hydrolysis [*e.g. (2b)*, *(2f)*, *(3a)*]. Another disadvantage is that foreign material from the sample that is still present in the extract also forms corresponding derivatives, and this can lead to complicated gas chromatograms that are difficult to interpret[79,80].

When the ECD or the N-TID is used, the liquid phase of the gas chromatographic column must be particularly stable to high temperatures, since even traces of volatile components or decomposition products (bleeding of the column) would soon coat the radioactive source of the ECD or the crystal of the N-TID and reduce the detection sensitivity. It is necessary to use highly purified silicone derivatives, which are stable at least up to 300 °C, and whose polarity can be varied by variation of their content of methyl, phenyl, trifluoroisopropyl, or cyanoethyl groups.

4. General Methods

Though the methods for the quantitative residue determination of individual, known herbicides are not always entirely satisfactory, the analyst often has several methods to choose from, and with enough experience, good results can be obtained through critical interpretation.

The difficulties are much greater in screening analyses for market control. This calls for both the identification and the quantitative determination of residues of herbicides covering a wide range of different chemical structures; as far as possible, moreover, the same procedure should be applicable to the control of fruit, vegetables, cereal products, and the derived processed food products.

The analytical possibilities here are limited by the large number of compounds to be detected, so that there are practically no alternatives to column chromatography for the clean-up and gas chromatography for the final determination. Though

the highly sensitive, specific detectors allow the analysis of extracts that have not been very highly purified, the gas chromatogram in this case, unlike in the individual determinations, must not contain additional peaks due to co-extractives from the plant material, since these could be misinterpreted as being due to residues of another pesticide. In addition to these methodological restrictions, the amount of time and work required for an analysis in the course of routine work must be as small as possible.

Moreover, the material to be analyzed is often in the form of large pieces (fruit, vegetables), and any residues may be on the surface or they may be very unevenly distributed in the interior. A precondition for a reliable analysis is therefore careful sampling in accordance with statistical principles so that the sample taken for analysis really is representative of the material under investigation.

The same analytical problem was encountered about ten years ago in the residue analysis of insecticidal chlorinated hydrocarbons and organophosphates as well as of a number of fungicides in foods from plants. Suitable multi-residue methods have now been devised for this purpose, and some have already been officially adopted[81-83]; these methods make use of a thermionic phosphorus detector (P-TID) and particularly the electron capture detector (ECD) for the final determination. The determination of insecticide and fungicide residues is now one of the routine analyses in food control.

Instead of carrying out separate analyses for herbicide residues, therefore, it is more logical to extend the procedures already used in order to detect as many pesticides as possible at the same time. However, in an analysis with such a wide scope, a general method cannot be expected to allow the detection and quantitative determination of every compound

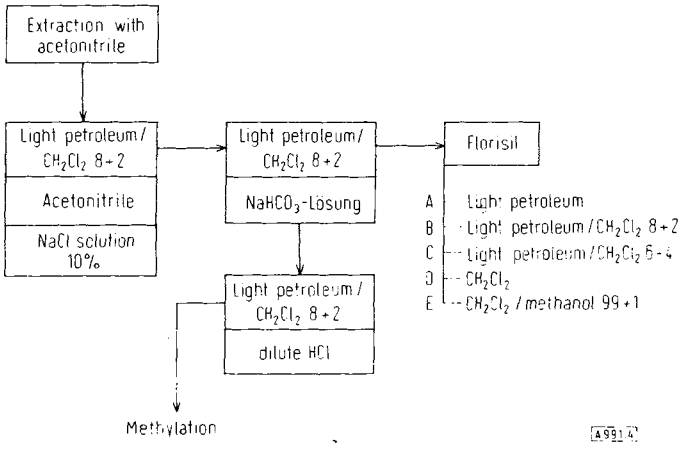


Fig. 4. Scheme for the clean-up [84] of plant material in a general method for residues of herbicides and other pesticides (see also Table 2).

can be achieved by suitable choice of this solvent, which should be just sufficiently polar to take up all pesticides, but as little as possible of the substances derived from the plant itself.

The herbicidal acids and phenols [*(5), (6), (9), (10)*] are separated from the organic phase by extraction of their salts into an aqueous solution. Without further clean-up these can generally be methylated with diazomethane and analyzed by gas chromatography with the ECD[85]. The neutral pesticides are purified by column chromatography on Florisil of suitably adjusted activity, which retains coloring matter and residual lipids particularly well. By elution with solvent mixtures of increasing polarity, it is possible to separate the pesticides so that chemically similar compounds are found in the same or neighboring fractions (Table 2).

Table 2. Fractionation of pesticides on a Florisil column, with the detectors used (A–E see Fig. 4. ECD = electron capture detector, P-TID and N-TID = thermionic detectors for phosphorus and for nitrogen respectively).

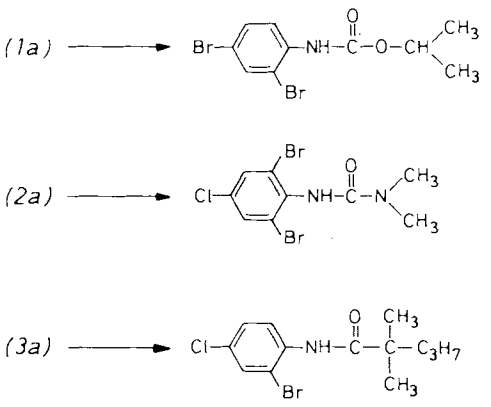
Pesticide group	Detector	Fraction				
		A	B	C	D	E
Insecticides and acaricides						
Chlorinated hydrocarbons	ECD	++	++			
Organophosphates	ECD, P-TID		++	++		++
Various fungicides	ECD	+	++	+		
Herbicides						
Triazines *(4)*	N-TID				++	
Carbanilic esters *(1)*	→ECD		+	+		
N-Phenylureas *(2)*	→ECD			++	+	
Anilides *(3)*	→ECD			++		

under optimum conditions. A compromise must therefore be adopted between the number of pesticides covered by the analysis, the detection sensitivity that can be attained, the recovery in the clean-up procedure, the possible separation of interfering substances, and the amount of work involved.

In an analytical procedure of this type (Fig. 4)[84], it is best to extract the plant material by homogenization with acetonitrile, since only a fraction of the plant lipids is then co-extracted. In the usual analyses for insecticides[81-83] this crude extract is diluted with a surplus of water and extracted with petroleum ether or methylene chloride. Since this must be expected to lead to losses of polar pesticides, it is better to dilute the crude extract with an organic solvent and then to remove acetonitrile and extracted water together with water-soluble substances of natural origin. An additional purification effect

In the gas-chromatographic examination of the various fractions, most of the insecticides and fungicides are detected with the ECD, the remaining organophosphates with the P-TID, and the triazines *(4)* and a few other herbicides with the N-TID. Bromo derivatives[86] of numerous herbicidal carbanilic esters *(1)*, *N*-phenylureas *(2)*, and anilides *(3)* are then prepared in the same fractions; these can also be analyzed with the ECD (Scheme 2).

The bromination conditions are so chosen that each herbicide forms only one monobromo or dibromo derivative, which is thermally stable and allows both identification and quantitative determination. This is achieved by reaction with bromine containing 5% of iodine (as a catalyst for aromatic substitution) for 10 min at room temperature in acetic acid or in the absence of solvent. Because of the high detection sensitivity



Scheme 2.

of the resulting bromo derivatives, it is possible to use such a high dilution that there is practically no interference due to residual organic matter from the sample (Fig. 5).

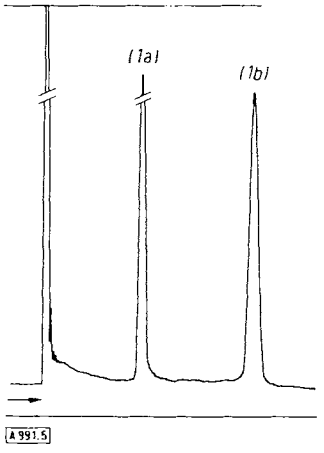


Fig. 5. Gas chromatogram of an extract from potatoes with 0.1 ppm each of propham (*1a*) and chlorpropham (*1b*) after bromination [86]. Operating conditions: 1 m 10% SE-30, 200 C, 120 ml/min of Ar (5% CH_4), ECD (^{63}Ni), 0.25 ng-equivalent of (*1a*) and (*1b*) injected.

Even with a great deal of experience, interference[187] and misinterpretations[24] cannot be ruled out in general methods of this type, where one is dealing with nanogram quantities and at the ppm to ppb level. The result should not therefore be regarded as certain unless it can be confirmed by a second analytical method (photometry, combination of gas chromatography with mass spectrometry[27], *etc.*).

5. Automation

Though investigations for herbicide residues involve a large number of individual analyses, few attempts have been made to automate the procedures. The photometric or gas-chromatographic final determinations would present no problems in this respect, since flow-type cells or automatic injection devices are available nowadays for continuous measurements, and there are integrators and computers of a suitable size for control and evaluation. However, the automatic clean-up of the samples still raises great difficulties.

A suitable apparatus has been designed for the residue analysis of some triazine derivatives (*4*)[49, 88, 89], and this could serve as a model for other similar determinations. It involves the extraction of 40 g of a soil sample with warm acetonitrile, precipitation of colloids with calcium chloride solution, evaporation of the solvent under mild conditions, and extraction of the residual aqueous solution with hexane/ether (2 : 1). The final determination is carried out by gas chromatography with the Coulson electrolytic conductivity detector; it is possible to deal with six samples per hour.

The extracts obtained in this way are sufficiently pure for analysis with a highly selective detector, but not for the electron capture detector (ECD), which is still indispensable for a general method. It would therefore be necessary, above all, to automate the column chromatography for the purification of the extracts, but no satisfactory solution to this problem has yet been found. The analyst has a wide scope here for the optimization of the known methods and for new ideas.

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[1] *H. Maier-Bode:* Herbizide und ihre Rückstände. Ulmer, Stuttgart 1971.

[2] *R. Wegler:* Chemie der Pflanzenschutz- und Schädlingsbekämpfungsmittel. Springer, Berlin 1970. Vol. 2.

[3] *H. Martin:* Die wissenschaftlichen Grundlagen des Pflanzenschutzes. Verlag Chemie, Weinheim 1967.

[4] *W. Koch:* Unkrautbekämpfung. Ulmer, Stuttgart 1970.

[5] *G. Corduan*, Mitt. Deut. Pharm. Ges. *40*, 29 (1970).

[6] *G. Zweig*, Residue Rev. *25*, 69 (1969).

[7] *J. B. Hanson* and *F. W. Slife*, Residue Rev. *25*, 59 (1969).

[8] *J. L. Anderson* and *W. W. Thomson*, Residue Rev. *47*, 191 (1973).

[9] Biologische Bundesanstalt für Land- und Forstwirtschaft, Braunschweig: Pflanzenschutzmittel-Verzeichnis, 23rd Edit. 1972; Verzeichnis der Wirkstoffe der zugelassenen Pflanzenschutzmittel, 3rd Edit. 1972.

[10] *H. M. Hull*, Residue Rev. *31*, 1 (1970).

[11] *P. C. Kearney* and *D. D. Kaufman:* Degradation of Herbicides. Dekker, New York 1969.

[12] *S. Matsunaka*, Residue Rev. *25*, 45 (1969).

[13] *R. P. Upchurch*, Residue Rev. *16*, 46 (1966).

[14] *P. C. Kearney* and *C. S. Helling*, Residue Rev. *25*, 25 (1969).

[15] *D. R. Cullimore*, Residue Rev. *35*, 65 (1971).

[16] Deutsche Forschungsgemeinschaft: Rückstandsanalytik von Pflanzenschutzmitteln. Verlag Chemie, Weinheim 1969.

[17] Höchstmengenverordnung Pflanzenschutz, pflanzliche Lebensmittel, of November 30, 1966 (BGBl. I, p. 667) in the form of June 5, 1973 (BGBl. I, p. 536).

[18] *R. Delley, K. Friedrich, B. Karlhuber, G. Szekely*, and *K. Stammbach*, Z. Anal. Chem. *228*, 23 (1967).

[19] *A. Calderbank*, Residue Rev. *12*, 14 (1966).

[20] *D. F. Lee, J. Britton, B. Jeffcoat*, and *R. F. Mitchell*, Nature *211*, 521 (1966).

[21] *R. C. Tindle*, J. Agr. Food Chem. *17*, 900 (1969).

[22] *W. W. Thornburg*, Residue Rev. *14*, 1 (1966).

[23] *H. Beckman* and *W. O. Gauer*, Residue Rev. *18*, 1 (1967).

[24] *J. R. Pearson, F. D. Aldrich*, and *A. W. Stone*, J. Agr. Food Chem. *15*, 938 (1967).

[25] *G. v. Unruh, G. Remberg*, and *G. Spiteller*, Chem. Ber. *104*, 2071 (1971).

[26] *T. R. Kantner* and *R. O. Mumma*, Residue Rev. *16*, 138 (1966).

[27] *F. J. Biros*, Residue Rev. *40*, 1 (1971).

[28] *C. E. McKone, T. H. Byast*, and *R. J. Hance*, Analyst *97*, 653 (1972).

[29] *R. Behrens*, Residue Rev. *32*, 355 (1970).

[30] *G. Zweig:* Analytical Methods for Pesticides, Plant Growth Regulators, and Food Additives. Academic Press, New York, Vol. 1 - 5, 1963 - 1967.

[31] *A. A. Akhavein* and *D. L. Linscott*, Residue Rev. *23*, 97 (1968).

[32] *E. Kröller*, Residue Rev. *12*, 162 (1966).

[33] *W. E. Bleidner*, J. Agr. Food Chem. *2*, 682 (1954).

[34] *W. Horwitz:* Official Methods of Analysis of the Association of Official Analytical Chemists. Washington, 11th Edit. 1970.

[35] *V. A. Joliffe* and *C. W. Coggins, Jr.*, J. Agr. Food Chem. *18*, 394 (1970).

[36] *A. W. Davidson*, J. Ass. Offic. Anal. Chem. *53*, 179 (1970).

[37] *C. Reinhard*, Deut. Lebensm.-Rundsch. *63*, 340 (1967).

[38] *W. Ebing*, Mitt. Biol. Bundesanst. Land. Forstwirt. *138* (1970), *143* (1972), *152* (1973).

[39] *G. Zweig*, Analytical Methods for Pesticides and Plant Growth Regulators. Academic Press, New York 1972, Vol. 6.

[40] *W. E. Westlake* and *F. A. Gunther*, Residue Rev. *18*, 175 (1967).

[41] *M. Krejčí* and *M. Dressler*, Chromatogr. Rev. *13*, 1 (1970).

[42] *D. Jentzsch* and *E. Otte*: Detektoren in der Gaschromatographie. Akademische Verlagsgesellschaft, Frankfurt 1970.

[43] *H. L. Pease*, J. Agr. Food Chem. *16*, 54 (1968).

[44] *C. C. Cassil*, *R. P. Stanovick*, and *R. F. Cook*, Residue Rev. *26*, 63 (1969).

[45] *D. M. Coulson*, J. Gas Chromatogr. *4*, 285 (1966).

[46] *G. G. Patchett*, J. Chromatogr. Sci. *8*, 155 (1970).

[47] *W. E. Westlake*, *A. Westlake*, and *F. A. Gunther*, J. Agr. Food Chem. *18*, 685 (1970).

[48] *W. P. Cochrane* and *B. P. Wilson*, J. Chromatogr. *63*, 364 (1971).

[49] *D. Eberle*, *D. Naumann*, and *A. Wüthrich*, J. Chromatogr. *45*, 351 (1969).

[50] *A. M. Mattson*, *R. A. Kahrs*, and *J. Schneller*, J. Agr. Food Chem. *13*, 120 (1965).

[51] *W. P. Cochrane*, *B. P. Wilson*, and *R. Greenhalgh*, J. Chromatogr. *75*, 207 (1973).

[52] *H. P. Hermanson*, *M. Siewierski*, and *K. Helrich*, J. Ass. Offic. Anal. Chem. *52*, 175 (1969).

[53] *J. H. Onley* and *G. Yip*, J. Ass. Offic. Anal. Chem. *54*, 1366 (1971).

[54] *C. A. Bache* and *D. J. Lisk*, Anal. Chem. *38*, 783 (1966); *39*, 786 (1967).

[55] *C. A. Bache* and *D. J. Lisk*, J. Ass. Offic. Anal. Chem. *50*, 1246 (1967).

[56] *C. A. Bache* and *D. J. Lisk*, J. Gas Chromatogr. *6*, 301 (1968).

[57] *W. A. Aue*, *C. W. Gehrke*, *R. C. Tindle*, *D. L. Stalling*, and *D. D. Ruyle*, J. Gas Chromatogr. *5*, 381 (1967).

[58] *C. H. Hartmann*, J. Chromatogr. Sci. *7*, 163 (1969).

[59] *W. Ebing*, Chromatographia *1*, 382 (1968).

[60] *V. V. Brazhnikov*, *M. V. Gur'ev*, and *K. I. Sakodynsky*, Chromatogr. Rev. *12*, 1 (1970).

[61] *M. Donike*, *L. Jaenicke*, *D. Stratman*, and *W. Hollmann*, J. Chromatogr. *52*, 237 (1970).

[62] *R. C. Tindle*, *C. W. Gehrke*, and *W. A. Aue*, J. Ass. Offic. Anal. Chem. *51*, 682 (1968).

[63] *L. Fishbein*, Chromatogr. Rev. *12*, 167 (1970).

[64] *H. J. Jarczyk*, Pflanzenschutz-Nachr. „Bayer" *25*, 21 (1972).

[65] *L. Fishbein* and *W. L. Zielinski, Jr.*, Chromatographia *2*, 38 (1969).

[66] *D. C. Fenimore* and *C. M. Davis*, J. Chromatogr. Sci. *8*, 519 (1970).

[67] *R. J. Maggs*, *P. L. Joynes*, *A. J. Davies*, and *J. E. Lovelock*, Anal. Chem. *43*, 1966 (1971).

[68] *W. L. Zielinski, Jr.*, *L. Fishbein*, and *L. Martin, Jr.*, J. Gas Chromatogr. *5*, 552 (1967).

[69] *H. P. Burchfield* and *D. E. Johnson*: Guide to the Analysis of Pesticide Residues. U.S. Department of Health Education, and Welfare, Washington 1965, Vol. 1.

[70] *M. Smith*, *H. Suzuki*, and *M. Malina*, J. Ass. Offic. Anal. Chem. *48*, 1164 (1965).

[71] *W. H. Gutenmann* and *D. J. Lisk*, J. Ass. Offic. Anal. Chem. *48*, 1173 (1965).

[72] *G. Yip* and *S. F. Howard*, J. Ass. Offic. Anal. Chem. *51*, 24 (1968).

[73] *J. M. Devine* and *G. Zweig*, J. Ass. Offic. Anal. Chem. *52*, 187 (1969).

[74] *W. H. Gutenmann* and *D. J. Lisk*, J. Agr. Food Chem. *11*, 304 (1963).

[75] *J. E. Scoggins* and *C. H. Fitzgerald*, J. Agr. Food Chem. *17*, 156 (1969).

[76] *A. Bevenue* and *J. N. Ogata*, J. Chromatogr. *46*, 110 (1970).

[77] *D. G. Crosby* and *J. B. Bowers*, J. Agr. Food Chem. *16*, 839 (1968).

[78] *I. Baunok* and *H. Geissbühler*, Bull. Environ. Contam. Toxicol. *3*, 7 (1968).

[79] *W. H. Gutenmann* and *D. J. Lisk*, J. Agr. Food Chem. *12*, 46 (1964).

[80] *A. Guardigli*, *W. Chow*, and *M. S. Lefar*, J. Agr. Food Chem. *20*, 348 (1972).

[81] See ref. [34], chapter 29.

[82] Méthodes officielles de recherche des résidus de pesticides. Journal officiel de la République Française, No. 68–191 of December 3, 1968.

[83] GDCh Working Group on Pesticides, 1st recommendation of March 1, 1971; Mitt. GDCh-Fachgruppe Lebensmittelchemie *25*, 129 (1971).

[84] *H.-P. Thier*, Deut. Lebensm.-Rundsch. *68*, 345 (1972).

[85] *H.-P. Thier*, Deut. Lebensm.-Rundsch. *66*, 393 (1970).

[86] *H.-P. Thier*, Deut. Lebensm.-Rundsch. *68*, 397 (1972).

[87] *D. E. Glotfelty* and *J. H. Caro*, Anal. Chem. *42*, 282 (1970).

[88] *D. E. Ott*, *G. Formica*, *G. F. Liebig, Jr.*, *D. O. Eberle*, and *F. A. Gunther*, J. Ass. Offic. Anal. Chem. *54*, 1388 (1971).

[89] *W. D. Hörmann*, *G. Formica*, *K. Ramsteiner*, and *D. O. Eberle*, J. Ass. Offic. Anal. Chem. *55*, 1031 (1972).

[90] *R. R. Laski* and *R. R. Watts*, J. Ass. Offic. Anal. Chem. *56*, 328 (1973).

[91] *C. Parouchais*, J. Ass. Offic. Anal. Chem. *56*, 831 (1973).

[92] *W. P. Cochrane* and *R. Purkayastha*, Toxicol. Environ. Chem. Rev. *1*, 137 (1973).

Trace Analysis of Organic Compounds

By Klaus Beyermann[*]

The trace analysis of organic compounds presents a number of additional difficulties in comparison with the trace analysis of inorganic compounds. Thus special problems arise in sampling and in the storage of samples (*e.g.* because of the instability of many organic compounds). It is also difficult to choose suitable mild separation methods and to find highly sensitive, molecule-specific determination methods.

1. Introduction

Very little attention has been given in the past to the trace analysis of organic components. For example, there are hardly any textbooks in this field, and the majority of lecturers at conferences on the subject deal with the (admittedly great) problems of the trace analysis of inorganic compounds. The relatively modest place allotted to this topic does not agree with the great importance of organic compounds, and is quite incomprehensible when one compares the number of these compounds with that of inorganic substances.

There are several conceivable reasons for this low level of representation. Thus possible explanations are that the trace analysis of organic compounds is not important, or that the trace analysis of organic compounds, though important, is very difficult.

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If one adopts the second view, there are two assertions that have to be proved:

1. the trace analysis of organic compounds is of great interest; and

2. the trace analysis of organic compounds raises problems that are even greater than the well-known difficulties of the trace analysis of inorganic compounds.

2. Interest in the Trace Analysis of Organic Compounds

The interest in the trace analysis of organic compounds can be demonstrated by the number of publications for 1972 reported in "Analytical Abstracts" (see Table 1).

Table 1. Classification of the analytical publications from the year 1972 reported in "Analytical Abstracts".

Area	Overall proportion [%]	Trace analysis [%]
Biochemistry	30	6
Organic chemistry	12	1
Food chemistry	9	2
Pharmaceutical chemistry	4	0
Air and water chemistry	3	1
Agricultural chemistry	3	1
Inorganic chemistry	25	8
Miscellaneous (instrumentation)	14	1
	100	

61% of all publications are concerned with the analysis of organic components. The greatest number (about 30%) are publications from the field of biochemical analysis. Only a relatively small number of articles are devoted to the analysis of components in drugs, in air, in water and effluents, and in agriculture. About 11% of the publications dealing with organic analysis are concerned with trace analysis. This corresponds to about 0.1% of all publications in the field of chemistry as a whole.

Further classification of the articles on the trace analysis of organic compounds reveals investigations on hormones, steroids, amino acids, physiological blood constituents, enzymes and amboceptors, and anesthetics (each of these groups accounting for about 1% of the publications) in the field of biochemistry. Important topics in connection with food analysis are determinations of residues from insecticides and hormones as well as other contaminating substances of animal or human origin.

Trace analyses of organic compounds play a relatively important part in the fields that are currently in the focus of public interest and that fall under the headings "protection of the environment" and "purity of food". It is clear, therefore, that there is great interest in the analysis of traces of organic components.

3. The Difficulties of the Trace Analysis of Organic Compounds

The comparatively small number of lectures and publications is therefore probably due to the difficulties of the trace analysis of organic compounds. Some examples will be given below in support of this assertion. A comparison with the problems of the trace analysis of inorganic compounds seems advisable, since there are more publications in this field and its difficulties are probably better known.

3.1. Difficulties in Sampling and in the Storage of Samples

The difficulties of sampling can be illustrated by the determination of the insecticide content of air. It is well known that after insecticides have been sprayed, they disappear in time either through chemical transformation or through physical processes, in most cases evaporation. Insecticides that can evaporate in this way have a correspondingly high vapor pressure. A certain insecticide content can therefore be anticipated in the air. It is likely that some of the insecticide will be held on dust particles, but because of its high vapor pressure it will also be present to an appreciable extent as a free component in the gas phase. Difficulties arise in the determination of this fraction in the ng/m^3 range, since condensation to reduce the vapor pressure results in the formation of aerosols, which cannot be quantitatively determined. The lower the temperature to which the gas sample is cooled for "quantitative" condensation, the smaller are the aerosol particles, with the result that the yields deteriorate.

One method that gives high yields even for nanogram quantities[11] involves the passage of the air containing insecticide through gauzes coated with polyethylene glycol. The nonpolar active substances dissolve in the polyethylene glycol with high yields, as can be shown by the use of ^{14}C-labeled insecticides. They can then be determined by gas chromatography. Examples of chromatograms of the total insecticide content in air samples are shown in Figures 1 and 2.

The fraction that is not in the form of aerosols amounts to many times the quantity that is associated with dust. If inhaled air and exhaled air are analyzed under identical conditions, distinctly lower insecticide concentrations are found in the latter (see Fig. 3).

The substances are partly deposited in the respiratory tract and absorbed into the body. The same results were found in (as yet unpublished) experiments with guinea pigs, which

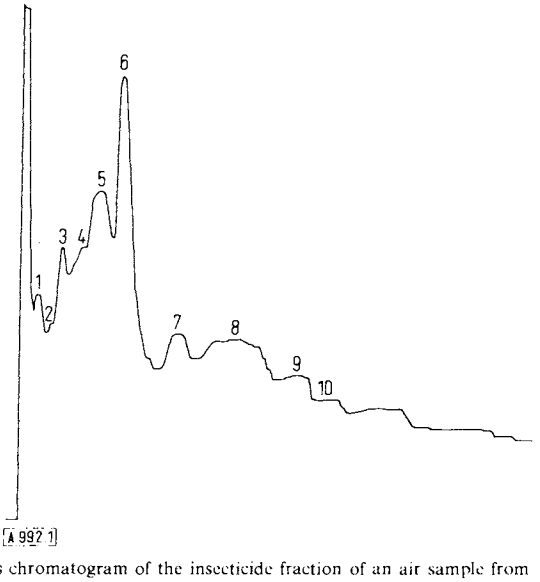


Fig. 1. Gas chromatogram of the insecticide fraction of an air sample from an agricultural area (Heidesheim near Mainz). Quantity of air investigated: 3 m^3. The contents found are about 170 ng/m^3 for aldrin and about 300 ng/m^3 for DDT. 1 = Phosdrin, 3 = CDEC, 5 = aldrin, 6 = daconil, 7 = ethylparathion, 8 = dieldrin, 9 = *o,p*-DDT; 2 and 4 have yet to be identified (after [1]).

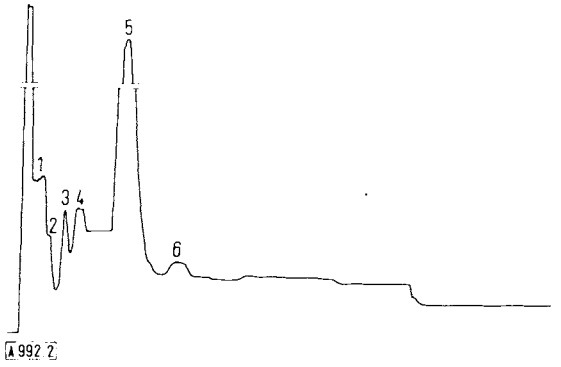


Fig. 2. Gas chromatogram of an air sample taken at the confluence of the Rhine and the Main. Conditions as for Fig. 1. 1 = Phosdrin, 3 = CDEC, 5 = daconil, 6 = ethylparathion; 2 and 4 have yet to be identified (after [1]).

clearly demonstrated the absorption of inhaled ^{14}C-labeled insecticides.

In the analysis of blood samples in clinical work, differences are often found according to the point from which the sample

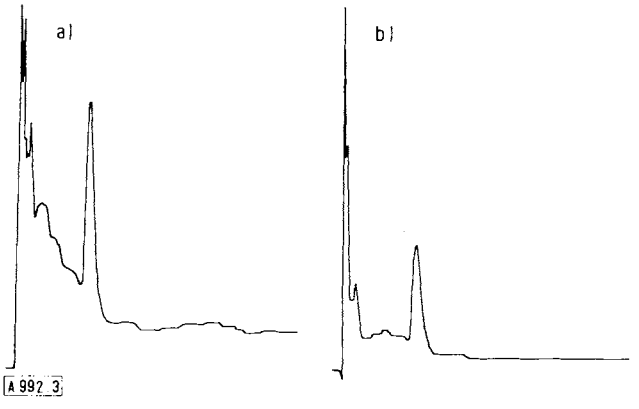


Fig. 3. Comparison of the insecticide content of a) inhaled and b) exhaled air under otherwise identical analytical conditions (after [1]).

was taken, since the concentrations of many substances in venous blood are different from those in arterial blood[2]. The sampling conditions, including the point from which the sample was taken, must therefore be indicated very precisely in analyses of this type.

The same problems arise in the storage of samples containing organic trace components as in the trace analysis of inorganic compounds, *i.e.* adsorption on the walls of the storage vessels.

Insecticides in water samples, for example, are adsorbed on the walls of polyethylene vessels after a very short time[3]. Quinine, which has to be analyzed in ng/ml concentrations by fluorescence spectroscopy in cells, is practically all situated on the wall of the glass vessel within seconds, even when the alkaloid solution is 0.1 N in sulfuric acid[4]. To avoid losses of this nature, it is recommended that the walls of the apparatus should be saturated with a solution of the trace component to be determined in a suitable concentration. It is better to keep the wall area of the vessel as small as possible in every case in order to minimize the adsorption effect. A change of solvent or of the composition of the test solution is also helpful in many cases.

Problems that are not found in the trace analysis of inorganic compounds arise because of the ease of decomposition, oxidation, or enzymatic-bacterial transformation of the samples to be stored. This is a serious problem in the storage of blood samples.

Though the literature data[5-8] are unfortunately rather contradictory, they show, for example, that the concentrations of bilirubin and of cholesterol change within two days even when the serum samples are stored at 3 C. The phosphate and ammonia contents of the blood samples increase rapidly, since organic compounds are decomposed with formation of these inorganic products.

The enzyme activities in blood or serum samples are also influenced by the manner in which the samples are stored. The activities of lactate dehydrogenases and phosphatases decrease within two days when the sample is kept at 0 °C. An entirely new problem to the trace analyst who has been concerned with inorganic compounds is presented by the behavior of some enzymes, whose suspensions in aqueous ammonium sulfate solution lose their activity on freezing and thawing[9].

This instability leads to problems of organization in clinical laboratories where a very large number of samples must be examined. Efforts are made to avoid bacterial decomposition by storage at −23 °C or by freeze drying, as well as by the addition of chemical stabilizers. However, this procedure is not entirely free from problems, since these additives can interfere with the analyses. The safest method is to work up the samples as soon as possible.

The problem of the instability of the samples is particularly serious where constant concentrations or activities of calibration standards must be maintained for long periods.

3.2. Digestion Methods

Digestion methods play a much greater role in the trace analysis of inorganic compounds than in the analysis of organic trace components. In particular, destructive digestion methods are rarely of any interest in the latter field.

On the other hand, sample preparation is very important in the disintegration of cellular tissues to liberate special components or to obtain selected cell fractions or particle fractions. The methods used here range from centrifugation in solutions of specified density, ultracentrifugation, and electrophoresis of whole cells to immunological methods.

The removal of the main component, protein, to obtain traces of low molecular weight substances is also a problematic step. It can lead to low values *e.g.* by occlusion of the trace components or as a result of their adsorption on the precipitated protein, but it can also lead to high values through removal of amino acids from the proteins (in amino acid analyses).

3.3. Separation Methods

The most critical step in the trace analysis of organic compounds lies in the choice of a suitable separation method. All the test materials in which great interest is shown (blood, tissue, food, urine, and apparently even systems as "simple" as air or water) are complicated and consist of a large number of principal and minor components. Separations are unavoidable in the great majority of cases.

A "preliminary" publication (more than 250 pages long) on the influence of 9000 drugs on the results of clinical analyses[10] shows that the "blood system" cannot by any means be regarded as a constant matrix. From the precision standpoint, therefore, the trace component in which one is interested should preferably be separated from this variable system for trace analysis.

Whether this conscientiousness is a waste of time in view of the fact that trace separations in organic analysis are generally associated with particularly poor yields is a decision that must be left to the investigator in each individual case. However, losses can often be very effectively recognized and taken into account by the isotope dilution method.

A serious problem in the separation of traces from biochemical sources is that many of these substances are hydrophilic. The only separation methods that can really be considered for them are consequently methods in which water is used as an essential component of the system.

The commonly used separation methods include the chromatographic methods, ion exchange, electrophoresis, immunoelectrophoresis, and a number of liquid-liquid partition methods. A recent survey is given by *Kienitz* and *Runge*[11].

Methods that are familiar from the trace analysis of inorganic compounds, such as coprecipitation, can occasionally also be useful in organic chemistry. Thus biogenic amines in ng/ml concentrations can be coprecipitated in very high yields as tetraphenylborates on creatininium tetraphenylborate[12] and separated from other components.

Nanogram quantities of amines can be isolated almost quantitatively and selectively from a crystalline KCl/NH_4Cl/creatinine mixture by extraction with methanol.

To improve the efficiency of separations, it is sometimes suggested that derivatives of the trace components should be prepared, *e. g.* in the field of ultramicropreparative gas chromatography. However, problems are often also encountered here, since the organic substances in microgram quantities react differently with the reagent present in a very large excess than in the usual, roughly stoichiometric ratios as in preparative organic chemistry. The disturbing influence of water is particularly drastic in some derivative formation reactions if the quantity of the trace component is small in comparison with the water films that are adsorbed even on small micro vessels (in microgram quantities). The result is a severe limitation of the separation methods.

In the trace analysis of organic compounds, especially in the biochemical field, there is one problem that is practically unknown to the trace analyst in inorganic chemistry. In organic materials, the components in which we are interested are often substances the chemical nature of which is largely unknown. Examples of such substances are the metabolites of drugs or the many substances that are excreted in the urine. Thus *Scott*'s research group[13], for example, is constantly finding new components by UV spectrophotometry that they cannot fully identify.

The detection of specific isomers is another problem that is fairly unusual in the trace analysis of inorganic compounds. In protein analysis, we are often interested in only one conformer of a protein.

Another interesting problem that is troublesome in analysis is the detection of a trace component in a specific "bound form". Thus in the blood, very many drugs are more or less strongly bound to certain blood proteins. In many cases, only the fraction that is not bound to protein is pharmacologically active. In analysis, one tries to use mild methods for separation, and as far as possible methods that do not disturb the equilibrium, such as ultrafiltration, gel filtration, or some types of dialysis.

3.4. Determination Methods

In the methods for the determination of organic trace components, serious problems are again encountered in addition to those found in the trace analysis of inorganic compounds. In the analysis of organic substances, meaningful results are nearly always obtainable only by molecule-specific determination methods. Elementary analysis in the trace and micro ranges gives only hints at best. For this reason, an extremely effective tool for the trace analysis of inorganic compounds, *i. e.* radiochemical activation analysis, is almost useless for the trace analysis of organic compounds.

With the aid of highly refined special procedures, however, the molecule-specific determination methods of instrumental organic analysis (UV, IR, NMR, and MS) can also be used for the investigation of submicrogram quantities.

A sensitivity increase of one to two powers of ten can often be achieved here by electronic averaging. The instruments often allow the accumulation of results with equal validity over a range of as much as four powers of ten. However, the times required then become unacceptably long (several weeks) in many cases.

Figure 4 shows the example of the investigation of 25 ng of tyrosine, with part of the IR spectrum of this compound. No spectrum can be recorded in the usual manner. If the region is scanned 2448 times and the data collected in an

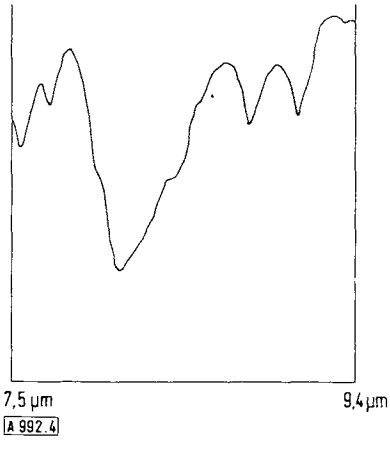


Fig. 4. IR spectrum of a sample of 25 ng of tyrosine after scanning of the range 2448 times and collection and processing of the data in an electronic averager (after [14]).

electronic averager, one finally obtains the spectrum shown, which is identical with the spectrum of larger quantities of tyrosine[14].

Mention should be made of the fundamental difficulty of most molecule-specific instrumental methods of analysis, *i. e.* that they require more or less pure substances. Preliminary separations thus acquire corresponding significance within

the analytical plan as a whole. After the trace component has been isolated (with the least possible loss), it must be quantitatively transferred into the instrument with the aid of micro techniques.

In addition to the spectroscopic methods mentioned, there are a large number of more or less molecule-specific methods. Thus gas chromatography is becoming increasingly reliable through the introduction of highly sensitive, element-specific detectors, and its results are easier to interpret.

Extremely high sensitivity, coupled in most cases with excellent specificity, is offered by enzymatic methods and immunological techniques. Among the latter, radioimmunoassay is at present often the only practicable possibility for the fast, specific determination of organic trace components in a large number of samples.

The method is based on the principle that the substance to be determined, which must act as an antigen, is allowed to react with a specific antibody. This antibody is added as the "reagent" in a substoichiometric quantity for the analysis. A small quantity of the substance to be analyzed, but in a radioactively labeled form, is also added to the sample. The antigen originally present in the sample itself and the added antigen compete to react with the substoichiometric quantity of antibody. If there is a large quantity of antigen that originally came from the sample, correspondingly less of the radioactively labeled antigen will be bonded to the antibody, and the activity found after isolation of the antigen-antibody complex is then a measure of the antigen concentration in the sample.

The analytical method depends on the availability of the radioactively labeled antigen and of the antibody, and it is necessary to verify that the latter reacts specifically and stoichiometrically with the antigen. Interference due to other plasma components, whose concentrations may vary, must be ruled out.

The effectiveness of the method was recently demonstrated once again in an example in which other methods of trace analysis were also compared[15]. This was the determination of digoxin and digitoxin in blood. About 10 to 20 % of people over 60 years of age require cardiotonic agents of this type. Because of their very narrow therapeutic range, it is desirable to know their concentration in the patient's blood. Thus good therapeutic results are obtained *e.g.* with digoxin in a concentration of 1 ng/ml of serum, but toxic effects appear at a concentration of 2 to 3 ng/ml. The objective determination of such low concentrations has until now been possible only by very complicated analytical methods; however, an elegant alternative is now offered by radioimmunoassay.

4. Closing Remarks

The trace analysis of organic compounds is a fascinating field, and is of great general importance. In addition to the difficulties of the trace analysis of inorganic compounds, the investigator in this field is very often faced with numerous other problems. Their solution calls for so much knowledge from neighboring fields that it seems justifiable here to consider analytical chemistry as an independent scientific field with interdisciplinary connections.

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Translated by Express Translation Service, London

[1] *K. Beyermann* and *W. Eckrich*, Z. Anal. Chem. *265*, 4 (1973).

[2] *R. Richterich:* Klinische Chemie. Akademische Verlagsgesellschaft, Frankfurt/M. 1965, p. 69.

[3] *L. Weil* and *K.-E. Quentin*, Gas-, Wasserfach, Ausg. Wasser-Abwasser *111*, 26 (1970).

[4] *S. Udenfriend:* Fluorescence Assay in Biology and Medicine. Academic Press, New York 1962, p. 101.

[5] *S. S. Wilson, R. A. Guillan*, and *V. E. Hocker*, Clin. Chem. *18*, 1498 (1972).

[6] *R. L. Kascht* and *V. A. Nelson*, Clin. Chem. *19*, 559 (1973).

[7] *H. Hofmeister* and *B. Junge*, Z. Klin. Chem. Klin. Biochem. *8*, 613 (1970).

[8] *O. Mühlfellner, G. Mühlfellner, P. Zöfel*, and *H. Kaffarnik*, Z. Klin. Chem. Klin. Biochem. *10*, 37 (1972).

[9] *H. U. Bergmeyer:* Methoden der enzymatischen Analyse. Verlag Chemie, Weinheim 1970, 2nd Edit.

[10] *D. S. Young, D. W. Thomas, R. B. Friedman*, and *L. C. Pestamer*, Clin. Chem. *18*, 1041 (1972).

[11] *H. Kienitz* and *H. Runge* in *F. Korte:* Methodicum Chimicum. Thieme, Stuttgart 1973, Vol. 1/2, p. 838.

[12] *K. Beyermann* and *F. Schredelseker*, Z. Anal. Chem. *256*, 279 (1971).

[13] *W. W. Pitt, C. D. Scott*, and *G. Jones*, Clin. Chem. *18*, 767 (1972).

[14] *K. Beyermann* and *J. Dietz*, Z. Anal. Chem. *268*, 197 (1974).

[15] *G. Bodem* and *H. J. Gilfrich*, Klin. Wochenschr. *51*, 57 (1973).

Chemically Produced Excited States

By Emil H. White, Jeffrey D. Miano, Carol J. Watkins, and Eves J. Breaux[*]

Electronically excited states of organic molecules are formed in many chemical reactions. Such chemically produced excited states are (with one exception) identical to light produced excited states, and they undergo the molecular transformations expected of such states ("photochemistry without light"). The excited states can also be used in energy transfer experiments. This review covers the generation of chemically produced excited states, the chemical reactions they undergo, and the possible role of chemically produced excited states in biology.

1. Introduction

Life on earth is dependent on a number of complex processes that utilize sunlight as the source of energy, the most important of which are probably photosynthesis, vision, photoperiodism, and phototaxis. In plants and animals, the sunlight that is absorbed forms electronically excited states of molecules; these excited states start chains of physical and chemical steps that lead to the synthesis of sugars, detection of the surroundings, setting of the biological clock, movement towards the sun, *etc.*[1]. In recent years it has been shown that the same excited states that are formed by the absorption of light can be produced by certain chemical reactions in total darkness. The present review will outline the generation, possible function, and uses of these chemically produced excited states.

2. Excited States

Electronically excited states (referred to hereafter as excited states) can be viewed as electron isomers of the stable forms of molecules and atoms; the stable forms are usually called ground states. Excited states have different distributions in space of their electrons as compared to the ground states (Fig. 1), and consequently they have different shapes, reactivities, and properties[2].

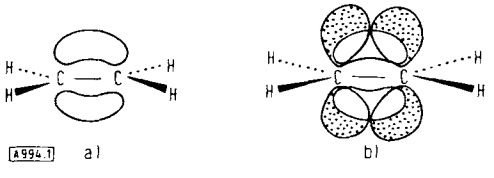


Fig. 1. Electron distribution in ethylene: (a) ground state, ○ = bonding orbital (contains two electrons); (b) first excited singlet state, ○ = bonding orbital, ⊖ = anti-bonding orbital (each contains one electron). Although not indicated, the geometries of the two states are different [2].

Energy is required to convert ground states into excited states. Thermal energy is often used to excite atoms, but most molecules would decompose before temperatures high enough to form excited states could be reached. Excited states of molecules are normally formed by the action of light in the visible and ultraviolet regions of the spectrum (Fig. 2, path 4), or by energy transfer from other excited molecules (equation 1, where the asterisk signifies the excited state).

Donor D* + Acceptor A → A* + D (1)

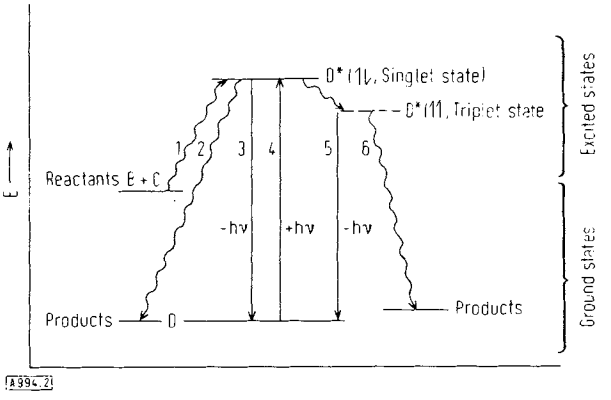


Fig. 2. Excited state processes [5]. Path 4: photoexcitation; 3 (or 4, 3): fluorescence; 4, 2: photochemical reactions; 5: phosphorescence; 1: chemical excitation; 1,3: chemiluminescence; 1,2 (1,6): "photochemistry without light".

Most ground states have fully paired electrons, as do excited states formed directly on absorption of light (such as that depicted in Fig. 1b). Molecules with all electrons paired are called singlet states.

A third general pathway for the formation of excited states exists, the direct formation in chemical reactions (Fig. 2, path 1)[3]. Such chemically produced excited states have been thought of largely as curiosities in the past; recent discoveries in this area, however, indicate a bright future for them[3,4].

Singlet excited states in liquid solutions have, with rare exceptions, very short lifetimes ($\approx 10^{-5}$—10^{-9} s)[5]. During this period of time they decay by one of several competing processes: 1) light emission and return to the ground state (Fig. 2, path 3); 2) chemical reaction (isomerization, dimerization, reaction with the solvent, *etc.*, Fig. 2, path 2); 3) energy transfer [eq. (1)]; 4) quenching, in which process the ground state is reached with release of the excess energy to the medium as heat; and 5) electron spin reversal, in which case a new excited state is produced bearing two electrons with parallel spins (called the triplet state) (Fig. 2). Triplet excited states are also highly reactive, decaying by the processes listed above. A summary of the above statements and an indication of the usual nomenclature is given in Figure 2.

3. The Chemical Generation of Excited States

It is possible that every chemical reaction yields some excited states. The excited states can be detected by the processes

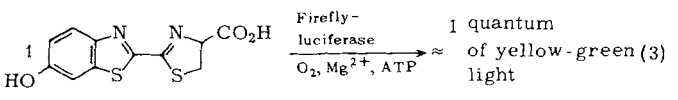
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outlined in the previous section. Measurement of the light emission (chemiluminescence) is the simplest and most sensitive method, however. By the criterion of chemiluminescence, even simple reactions such as the neutralization of acids and bases[6] and amide formation[7] (equation 2) have been shown to yield excited states.

$$2C_6H_5NH_2 + C_6H_5COCl \rightarrow C_6H_5CONHC_6H_5 + C_6H_5\overset{\oplus}{N}H_3Cl^{\ominus} \qquad (2)$$

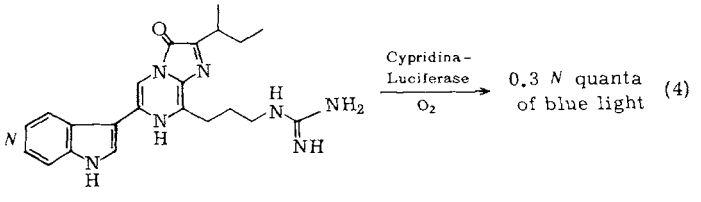
The above reactions are very inefficient in the production of excited states, however, and very sensitive counters are required to detect them. Quantum yields (Φ_{cl} = photons emitted/molecules reacted) of about 10^{-15} have been reported for simple chemical reactions of this type[6].

In contrast, several chemical reactions are efficiently chemiluminescent and bright light emissions are possible[8]. Many of these reactions produce light more efficiently than any commercial unit utilizing electrical energy[9]. Topping the list is the enzyme catalyzed air oxidation of firefly luciferin, which has been reported to be effectively 100% efficient in the overall process of light production [eq. (3)][10]. The efficiencies of



(3)

two other bioluminescent systems have also been measured *in vitro*. The reaction employed by the ostracod *Cypridinia* is ≈30% efficient in light production [eq. (4)][11], and the

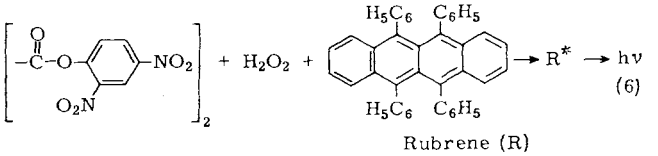


(4)

reaction employed by the luminous bacterium *Photobacterium fischeri* [eq. (5)] is reported to be about 5—10% efficient[12].

$$N\,RCHO \xrightarrow[O_2,\,FMNH]{\text{Enzyme}} < 0.1\,N \text{ quanta of bluish light} \qquad (5)$$

The most efficient *chemiluminescent* system reported to date (not involving enzymes) is the hydrogen peroxide-oxalate ester reaction in the presence of rubrene as the energy acceptor and ultimate light emitter [eq. (6)][13]. Under optimum condi-



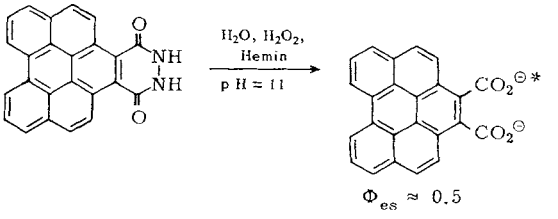
(6)

tions, 0.23 N photons are emitted per N molecules of ester that react. This and related systems are now the basis of a commercial chemiluminescent light generator.

Although the efficiency of light emission is important in chemiluminescence, the quantity of interest in the present review is the efficiency of the chemical production of excited states, Φ_{es}. The overall efficiency of chemiluminescence, Φ_{cl}, is a product of three efficiencies [eq. (7)],

$$\Phi_{cl} = \Phi_r \Phi_{es} \Phi_{fl} \qquad (7)$$

Φ_r, the fraction of reacting molecules that pursue the correct chemical pathway, Φ_{es}, defined above, and Φ_{fl}, the efficiency of fluorescence of the ultimate light emitter in the reaction. Since Φ_{cl} and Φ_{fl} are directly measurable, $\Phi_r\Phi_{es}$ can be readily determined. For reactions that produce high chemical yields of the light emitters, Φ_r has been assumed to be ≈ 1, permitting an estimate of Φ_{es}[14]. The highest value of Φ_{es} found to date for a non-enzymatic chemiluminescent reaction is ≈0.5 (50% efficient), a value reported for the light emission of a cyclic hydrazide based on perylene [eq. (8)][15a]. Recently, other quite different systems have been shown to yield chemically produced excited states with high efficiencies (20 to 100%)[15b].



(8)

It is thus apparent that some chemical reactions produce excited states quite efficiently. It would be valuable to be able to predict which reactions or reaction types in solution are in this category. In the gas phase, the known chemiluminescent reactions are sufficiently varied that no general relationships have been established other than the requirement that sufficient energy be available to form the excited states. For chemical reactions in solution, other variables are involved. Most organic reactions proceed in several steps with the formation of several intermediates. Normally, the individual steps are not energetic enough to form excited states of the immediate product formed (in contrast to many gas phase reactions). However, two general exceptions to this somewhat pessimistic statement have appeared in the past decade; two reaction types that lead efficiently to excited states have been discovered. The first is the thermal decomposition of 1,2-dioxetanes and the second is the one electron transfer reaction of radical anions and cations. Most of the known efficient chemiluminescent reactions proceed by one of these two processes; both will be outlined in later sections of this paper. Further research on chemical energy generation will undoubtedly reveal still other fundamental reaction mechanisms leading to excited states[16].

1,2-dioxetane

We will be concerned in this review principally with the reactions that generate excited states efficiently, particularly those carried out in liquid solutions since these systems permit energy transfer to large molecules of chemical and biochemical interest. A brief section on gas phase chemiluminescence is included, however, to exemplify the added physical information that can be obtained from simpler systems.

3.1. Gas Phase Reactions

Chemiluminescent reactions in the gas phase generally involve light emission by atoms or small molecules[17]. These reactions are of interest because of their occurrence in flames and in the upper atmosphere. The emission spectra frequently show considerable detail, which permits identifying the vibrational level as well as the electronic state of the emitting molecule. For example, the reaction of atomic oxygen with acetylene or carbon suboxide leads to three different excited states of carbon monoxide. The following reaction was proposed for the chemiluminescence[17b]:

$$O(^3P) + C_2O(^3\Sigma) \rightarrow CO(A^1\Pi, d^3\Delta, c^3\Sigma) \rightarrow h\nu \qquad (9)$$

Vibrational levels of up to $v'=9$ were observed for the excited states formed by this pathway[17b], whereas other pathways for the formation of CO in the acetylene oxidation have led to values of v' up to 33[18]. Laser emission by vibrationally excited CO has been observed recently in the atomic oxygen-acetylene reaction[19].

The reaction of basic solutions of hydrogen peroxide with chlorine leads to the formation of excited states of oxygen, which emit in the infrared region of the spectrum[20]. Visible

$$H_2O_2 + Cl_2 + NaOH \rightarrow \begin{array}{l} O_2(^1\Delta_g) \rightarrow h\nu(1.27\,\mu m) \\ + \\ O_2(^1\Sigma_g^+) \rightarrow h\nu(0.762\,\mu m) \end{array} \qquad (10)$$

light is also emitted; the pooling of energy by two excited states in contact dimers has been proposed to account for this fact[20, 21]. Emission from vibrationally excited levels was also seen. The singlet oxygen ($^1\Delta_g$ and $^1\Sigma_g^+$) and the encounter

$$\begin{array}{l} (O_2\,^1\Delta_g)_2 \rightarrow h\nu\,(634\,nm) \\ (O_2\,^1\Delta_g + O_2\,^1\Sigma_g^+) \rightarrow h\nu\,(478\,nm) \end{array} \qquad (11)$$

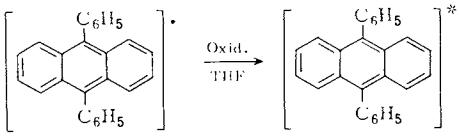
complexes apparently exist in and emit light from bubbles of oxygen gas which arise from the reaction mixture. If a fluorescent acceptor such as violanthrone[22] is added to the system, the overall light emission becomes much brighter. In this case, energy transfer from the singlet oxygen occurs, and since violanthrone is far more efficient in fluorescence than the various emitting forms of oxygen, more light is produced.

A number of gas phase chemiluminescent reactions occur in the upper atmosphere. Perhaps the most studied is the "air afterglow", which was first noted as a long lived yellow-green emission from electrical discharges in air. The afterglow involves an emission from excited nitrogen dioxide[23]. This reaction is used as a secondary standard for measuring quantum yields in chemiluminescence[24, 25] and as a means of measuring the concentrations of oxygen atoms[26].

$$NO + O \rightarrow NO_2^* \rightarrow h\nu \qquad (12)$$

3.2. Chemically Produced Excited States by Electron Transfer

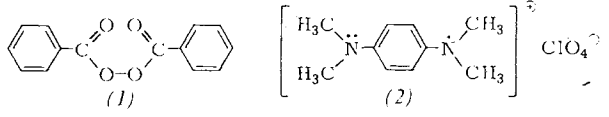
The formation of excited states by electron transfer has proven to be an excitation method of wide applicability. In this



(13)

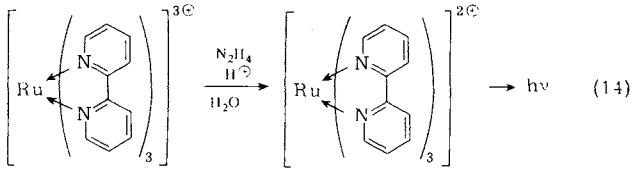
method, excited states are formed by the removal of an electron from a radical anion [eq. (13)], by the addition of an electron to a radical cation, or by cation-anion annihilation[27, 28]. In most of the cases studied, the excited state is capable of light emission and the overall process represents a simple example of chemiluminescence.

The precursor radical anions are usually prepared by the reaction of alkali metals with aromatic and heterocyclic compounds. Oxidation of the anions thus generated (to yield excited states) is often carried out with benzoyl peroxide *(1)* or Wurster's blue perchlorate *(2)*, although many other oxidizing agents have been used.



(1) *(2)*

Radical cations can be prepared from aromatic and heterocyclic compounds by oxidation with sulfuric acid, silver ion, *etc.* Reduction of the radical cations then leads to excited states, a wide variety of reducing agents having been used. In a reaction related to the reduction of radical cations, metal chelates such as tris(2,2'-bipyridyl)ruthenium(III) have been reduced with hydrazine [eq. (14)] or aqueous base to give chemiluminescence[28].



(14)

Radical anions and cations can also be formed electrolytically. The excitation step (anions $-1e$; cations $+1e$) can also be carried out at electrodes, and where controlled potential techniques are applicable, the energy input can be set at any value over a continuous range. The electrolytic method may simplify the chemiexcitation process by reducing the number of reagents in solution. However, the introduction of an electrode means that the reaction is no longer homogeneous; adsorption and local concentration effects must therefore be taken into consideration. Alternating current electrolysis can be used for the alternating production of anions and cations at the same electrode[29]; this method increases the probability of cation-anion annihilation. In a double potential step experiment, potentials of the alternating current can be set independently of each other for maximum efficiency of production of the cations and anions[27]. Cation-anion annihilation has been studied using a.c. electrolysis on such compounds as anthracene, 9,10-diphenylanthracene, perylene, rubrene, quaterphenyl, and 1,1,4,4-tetraphenylbutadiene[29].

Two possible processes for electron transfer excitation involving a cation and an anion of the same compound are shown schematically in Figure 3[27]

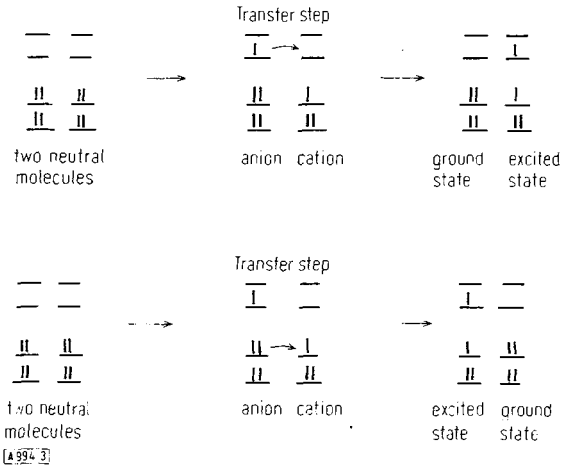


Fig. 3. Chemiexcitation *via* cation-anion annihilation.

Chemiexcitation *via* electron transfer may take more than one step, however. The multiplicity of the initial excited state is not known for any case, but the emitting species can be either a singlet or a triplet. Chemiluminescence has been observed from the following species during radical ion recombination reactions (where $A^{\ominus}$ is an anion and $C^{\oplus}$ is a cation)[30]: $^1A^*$, $^1C^*$, $^3A^*$, $^3C^*$, and $^1(A^{\ominus}C^{\oplus})^*$. In most cases, the spectrum of the light emitted matches the fluorescence spectrum of the emitting molecule, indicating that the emitter is an excited singlet. Triplet emission has been reported for the oxidation of the radical anions of phenanthrene *(3)*[31] and *N*-phenylcarbazole *(4)*[32a]. In the former case, it was

(3) *(4)*

proposed that efficient oxygen scavenging permitted detection of the phosphorescence. In the latter case, the emission may have been misidentified, since the observed emission is similar to the fluorescence of carbazole anion, which could have been formed by cleavage of the N—phenyl bond by the alkali metal used to make the radical anion[32b].

Electron transfer reactions represent a unique type of chemiexcitation in that the formation and destruction of chemical bonds are not involved in the excitation step[3]. Thus, this method would be expected to be a favorable case for the study of chemical excitation mechanisms. This process has been extensively studied, and several mechanisms have been proposed for the excitation process[27, 28, 33–35]. Cation-anion

$$A^{\ominus} + C^{\oplus} \rightarrow {}^1A^* + C \quad \text{(a)} \qquad (15)$$
$$A^{\ominus} + C^{\oplus} \rightarrow {}^1C^* + A \quad \text{(b)}$$

$$A^{\ominus} + C^{\ominus} \rightarrow {}^3A^* + C \quad \text{(a)}$$
$$A^{\ominus} + C^{\ominus} \rightarrow {}^3C^* + A \quad \text{(b)}$$
$$^3A^* + {}^3C^* \rightarrow {}^1A^* + C \quad \text{(c)} \qquad (16)$$
$$^3A^* + {}^3C^* \rightarrow {}^1C^* + A \quad \text{(d)}$$
$$^3A^* + {}^3A^* \rightarrow {}^1A^* + A \quad \text{(e)}$$
$$^3A^* + {}^3A^* \rightarrow {}^1C^* + C \quad \text{(f)}$$

annihilation, *e.g.*, could lead to an excited singlet directly [eq. (15)] or through annihilation of initially formed triplets [eq. (16)]. Cation-anion annihilation involving two different species may proceed *via* a charge-transfer complex [eq. (17)].

$$A^{\ominus} + C^{\oplus} \rightarrow (A \cdot C)^* \qquad (17)$$

One example of this type of charge-transfer complex is seen in the fluorescence emission observed from solutions of salts of the *N*-(2,6-dichlorobenzyl)quinolinium ion *(5)*, such as the iodide, bromide, thiocyanate, azide, or nitrite[36].

(5) *(6)*

In some cases[37], the energy produced by a single electron transfer reaction would appear to be insufficient to account for the energy emitted. A radical-ion aggregate mechanism involving multiple electron transfers with the transferred energy localized on one molecule (or ion) of the aggregate has been suggested to account for these observations[27, 34, 38]. *Freed* and *Faulkner*[35, 15b] have provided evidence for the intermediacy of the triplet state in the "energy-deficient" electron transfer reactions of fluoranthene *(6)*. Triplet-triplet annihilation could result in the formation of an excimer [eq. (18)] which could subsequently emit light. *Weller* and *Zachariasse*[39] have shown for a number of aromatic systems that sufficient energy should be available directly from electron transfer to populate the triplet but not the singlet excited state, thus favoring eq. (16) over eq. (15) for those cases. Furthermore, they observed dimethylanthracene excimer emission not due to excimers formed from excited singlet and ground state molecules [eq. (19)]. This observation suggests that the excimers were formed by triplet-triplet annihilation [eq. (18)], which in turn indicates the possibility of other triplet-triplet annihilation reactions forming excited singlets [eq. (16c), (16d) (16e) (16f)].

$$^3A^* + {}^3A^* \rightarrow {}^1A_2^* \qquad (18)$$

$$^1A^* + A \rightarrow {}^1A_2^* \qquad (19)$$

$$A^{\oplus} + A^{\ominus} \rightarrow {}^1A_2^* \qquad (20)$$

A third possible way of forming an excimer would be directly from the electron transfer reaction [eq. (20)]. Such an excimer mechanism has been suggested[40] for the oxidation of 9,10-diphenylanthracene radical anions. However, this process is probably not of major importance in producing chemiluminescence[41].

Chemiluminescence has been seen in double potential step experiments after one type of ion has been produced but before sufficient voltage has been applied to produce the ion of opposite charge. This "preannihilative emission" has been attributed to radical-ion aggregates, heterogeneous electron transfer at an electrode, or impurities in the solution[27, 41, 42].

Electron transfer reactions can lead to either ground state or excited state products depending on the configuration of the reactants, since the potential energy surface of the reactants may cross various product states at different configurational arrangements (Fig. 4)[28]. The probability of a particular reaction is related to the differences in free energy and configuration between product and reactant curves. The theoretical estimation of rates of formation of various products has been developed by *Marcus*[33] and reviewed by *Hercules*[41]. The expression for the rate constant is:

$$k = Z\kappa\rho\exp(-\Delta F^*/kT) \qquad (21)$$

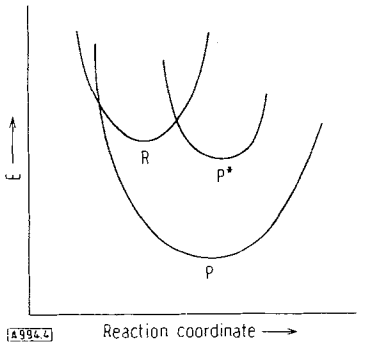


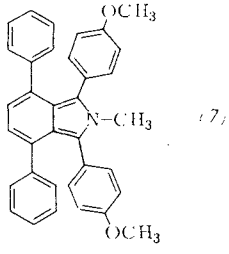
Fig. 4. Crossing between energy surfaces (R = reactants, P = products).

where Z is a diffusion-controlled rate constant, about 10^{11} l mol^{-1} s^{-1}, κ and ρ are usually about 1, and ΔF^* is an indication of the accessibility of the intersection [eq. (22)]:

$$\Delta F^* = w^r + \lambda/4\,[1+(\Delta F_R^{0'}/\lambda)]^2 \quad (a)$$
$$\Delta F_R^{0'} = \Delta F^{0'} + w^p - w^r \quad (b) \qquad (22)$$

In the above equations, w^r is the work required to bring the reactants together to the most probable separation distance in the activated complex, w^p is the work required to bring the products to the same separation distance, $\Delta F^{0'}$ is the standard free energy of the reaction under the given conditions, and λ is a reorganization term dependent on the differences in bond lengths and orientation polarization in the states just preceding and following electron transfer.

Early studies indicated that the quantum yields for such transfers were low. For example, a maximum efficiency of 0.3% was reported for the conversion of electrical energy to light using 1,3-bis(4-methoxyphenyl)-*N*-methyl-4,7-diphenylisoindole *(7)*[27]. Since the fluorescence quantum



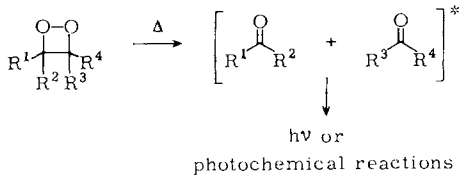
(7)

yield for this compound is 0.50, this figure corresponds to 0.6% efficiency for conversion of electrical energy to excited singlets. Recently, however, considerably higher quantum yields have been reported[43].

3.3. Chemically Produced Excited States from Dioxetanes

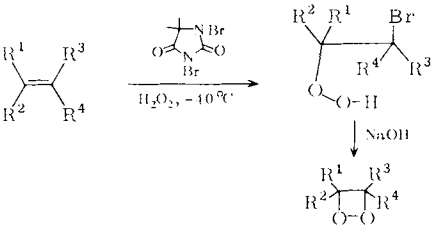
The important role of 1,2-dioxetanes in chemiluminescence has been established only recently. The dioxetane ring was first proposed as a critical intermediate in the oxygen-dependent chemiluminescent reactions of the lophines (arylimidazoles)[44], indoles[45], acridine compounds[46], peroxalates[47], and aminoethylenes[48], largely on the basis of the products formed and the likely pathways for their formation. Dioxetanes have also been proposed as intermediates in the bioluminescence of the firefly[49] and the crustacean *Cypridina hilgendorfii*[50].

In 1968, the first dioxetane was synthesized and characterized by *Kopecky* and *Mumford*[51]. They showed, also, that dioxetanes decompose to give excited states of the carbonyl products formed [eq. (23)], thus confirming the earlier hypothesis.



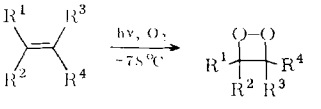
(23)

Several synthetic routes have been employed in the synthesis of 1,2-dioxetanes. The route of *Kopecky et al.*[52] involves the intramolecular displacement of a halogen by the hydroperoxide group [eq. (24)].



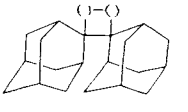
(24)

A second route utilizing singlet molecular oxygen was developed by *Bartlett, Schaap et al.*[53] and independently by *Foote* and *Mazur*[54]. They found that electron rich olefins lacking available allylic hydrogens react with singlet oxygen to give 1,2-dioxetanes [eq. (25)]. *Schaap* and *Bartlett* have also used triphenyl phosphite ozonide to imitate the singlet oxygen



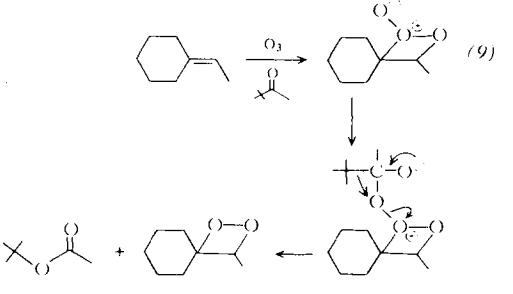
(25)

reaction with olefins[55]. Singlet oxygen generated by the methylene blue sensitization of molecular oxygen was used in the synthesis of peroxides of 2,2'-biadamantylidene *(8)*, a very



(8)

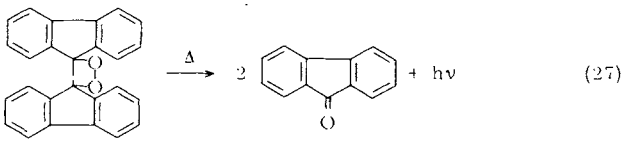
stable dioxetane[56]. Finally *Story et al.*[57] have reported that ozonolysis of olefins in solvents which readily undergo Baeyer-



(9)

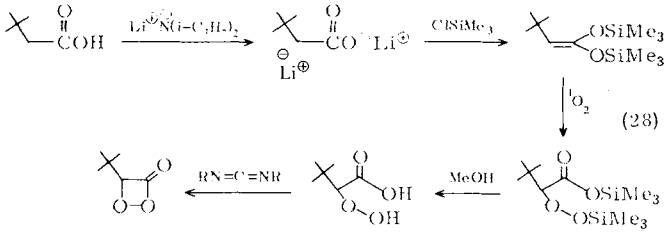
(26)

Villiger oxidation is a synthetic route to 1,2-dioxetanes. Their proposed mechanism postulates the molozonide *(9)*[58] described by *Staudinger* as the key intermediate [eq. (26)]. *Yang* and *Carr*[59] have reported using this method to synthesize the 1,2-dioxetane of 9,9'-bifluorenylidene, which according to the authors decomposes upon heating to give fluorenone and light [eq. (27)]. It should be noted, however, that *K. R. Kopecky et al.* have recently questioned the claim that dioxetanes are formed in ozonolyses[60].



(27)

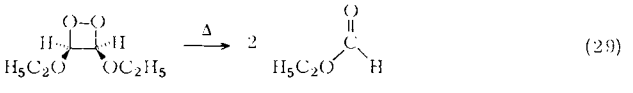
A derivative of a 1,2-dioxetane, a 1,2-dioxetanone, has recently been prepared by *Adam* and *Liu*[61] [eq. (28)]; however, efforts to isolate the compound in pure form were unsuccessful. Lastly,



(28)

Bollyky[67] has postulated the formation of 1,2-dioxetanones in chemiluminescence from the reactions of singlet oxygen with ketene and diphenylketene.

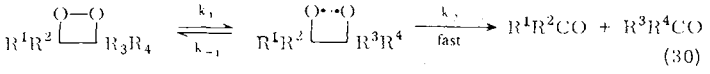
Kopecky and *Mumford*'s discovery that the thermal decomposition of 1,2-dioxetane leads to excited state carbonyl products prompted investigation into the nature of these products. *White*, *Wiecko* and *Wei*[4b] reported that the decomposition of trimethyl-1,2-dioxetane gave a 5% yield of a triplet carbonyl product based on the products formed. *Wilson* and *Schaap*[53d] studied the decomposition of *cis* diethoxy-1,2-dioxetane, which gives excited ethyl formate [eq. (29)]. They reported that



(29)

thermal decomposition was first order and gave the excited product in the triplet state (presumably *via* ethyl formate singlet precursors, cf. ref.[62]) with 20—100% yield based on observations of the sensitized fluorescence of dibromoanthracene and diphenylanthracene. Finally, *Turro* and *Lechtken*[62] have shown that the thermal decomposition of tetramethyl-1,2-dioxetane efficiently and selectively yields acetone triplets and that the triplets are not formed from excited singlet precursors *via* intersystem crossing. Their yield of singlet acetone was less than 1%, while the yield of triplet acetone was about 50% (error range ±50%).

Several explanations have been published in an attempt to rationalize why 1,2-dioxetanes should decompose thermally to give electronically excited products. *Rauhut*[47] has suggested that from energy considerations alone, it would appear that reactions involving a highly exothermic discrete step which directly yields small product molecules having few bonds capable of accepting vibrational energy could have potential for electronic excitation. Energy considerations alone do not explain all of the facts, however, for there are large complicated molecules (such as the luciferins) with many bonds and vibrational modes that form excited states *via* dioxetane intermediates[49, 50]. Thus, additional factors must be involved. Two mechanisms have been considered for the thermal decomposition of 1,2-dioxetanes: a biradical and a concerted mechanism. *Richardson et al.*[63] have proposed a biradical mechanism [eq. (30)] on the basis of rates of decomposition of dioxetanes



(30)

coupled with thermodynamic calculations. They proposed that in a two step mechanism—with the first step rate determining—resonance interactions by substituents would be unimportant, while these effects could influence the rate of the concerted mechanism where π-carbonyl character may be developed in the activated complex. This expectation was based on an analogy of the dissociation kinetics of alkyl-substituted cyclobutanes compared to acyl- and carboxyl-substituted cyclobutanes. *Richardson et al.* found that compounds *(10)* and *(11)* have the same rate: this result is consistent with the two step biradical process (Table 1).

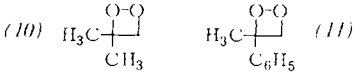


Table 1 [63]. Measured activation constants for the decomposition of *(10)* and *(11)*.

Cpd.	E_a [kcal/mol]	$\Delta H^{\neq}$ [kcal/mol]	$\Delta S^{\neq}$ [eu]
(10)	23.0±0.1	22.4±0.1	−5.0±0.2
(11)	22.9±0.2	22.3±0.2	−5.3±0.9

Values of the activation constants were also calculated and these were found to be in good agreement with the observed activation parameters (Table 2)[63].

Table 2 [63]. Calculated activation constants for the decomposition of *(10)* and *(11)*.

Cpd.	E_a [a]	$\Delta S^{\neq}, k_{-1}$ [eu]	$\Delta S^{\neq}$ [eu]	$10^4\ k$ [s^{-1}] 60°C
(10)	22.9	−5.4	−2.3	72
(11)	22.9	−5.9	−2.8	44

[a] kcal/mol with $E_{-1} = 8.5$ kcal/mol.

Richardson and *O'Neal* have calculated thermochemical and activation parameters for several methylated derivatives of 1,2-dioxetanes[64a, 66] and 1,2-dioxetanones[64b] based on the biradical two step mechanism. The calculations indicated that increased methyl substitution increases the stability of 1,2-dioxetanes. These authors have also calculated the available energies from the decomposition of 1,2-dioxetanes (Table 3). To reach an excited state, the sum of the heat of reaction for a 1,2-dioxetane giving carbonyl products ($-\Delta H_r^0$) and E_1 (the activation energy) must be equal to or greater than the energy difference between the 0 vibrational level in the

Table 3. Calculated available energies from the decomposition of 1,2-dioxetanes [64a, 66].

1,2-Dioxetane	ΔH_f^0 [kcal/mol] [a]	$(E_1 - \Delta H_f^0)$ [kcal/mol]
Unsubstituted	−55.4	76.9
1-Methyl	−58.8	80.5
1,1-Dimethyl	−61.1	84.0
1,2-*cis*-Dimethyl	−63.2	84.9
Trimethyl	−65.6	89.3
Tetramethyl	−68.8	93.5

[a] $\Delta H_r = H_f^0$ (1,2-dioxetane) $- \Delta H_f^0$ (carbonyl products).

first excited state of the carbonyl product and the ground state.

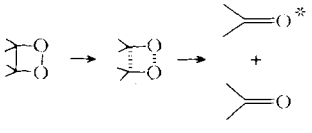
Richardson cites 81—87 kcal/mol[65] as this apparent threshold and shows that all but the unsubstituted dioxetane in Table 3 have sufficient energy[64a, 64b]. *Bollyky*[67] has independently calculated the decomposition energies of four dioxetane derivatives by the EHMO method (Table 4).

Table 4. Decomposition energy of dioxetanes as calculated by the EHMO method [67].

Dioxetane	Products	Calc. energy [kcal/mol]
Unsubstituted	Formaldehyde	−197
Tetramethoxy	Dimethyl carbonate	−206
-one	CO_2, formaldehyde	−184
-dione	CO_2	−132

He concludes that dioxetanes which contain at least one sp^2 carbon appear to have lower decomposition energies and thus have increased stabilities and lifetimes. However, *Adam et al.*[61a, 61b] have presented experimental evidence contrary to this conclusion.

The other major mechanism possible for the first order decomposition of 1,2-dioxetanes is the concerted mechanism. *McCapra*[3c, 68] suggested that the concerted decomposition of a 1,2-dioxetane should produce a carbonyl group in an excited state (antibonding) [eq. (31)], on the basis of ideas provided



(31)

by *Woodward* and *Hoffmann*[69] on orbital symmetry. *McCapra* suggested, further, that charge transfer might be playing a significant part in the excitation, perhaps allowing a mixing of states and providing a lower pathway for the excitation[3c]. Both *Kearns*[70] and *McCapra*[3c] have attempted to rationalize the decomposition of 1,2-dioxetanes by means of orbital correlation diagrams. *Kearns*' orbital correlation and state correlation diagrams for the decomposition of a 1,2-dioxetane are shown in Figures 5 and 6[70c]. According to the orbital correlation diagram, *Kearns* explains that the ground state electronic configuration of the dioxetane ($\ldots\sigma_{CC}{}^2\pi_{OO}{}^{*2}$) correlates with a highly excited electronic state of the carbonyl products[68, 70b]. "The lowest excited singlet and triplet states with electronic configuration $\ldots\pi_{OO}{}^{*1}\sigma_{OO}{}^{*1}$ are, however, stabilized by cleavage of the O—O bond"[70c]. As shown in the state correlation diagram (Figure 6), there is a crossing of curves which would allow the dioxetane to go over into an excited state of the product. While small distortions from C_2 symmetry would prevent crossing of the ground state curve with an excited singlet state, crossing of an excited triplet state curve could occur. *Kearns* suggests that one of the carbonyl ketones may be left in an excited triplet state as a result of the curve crossing, and that dioxetanes should be photochemically unstable with respect to cleavages.

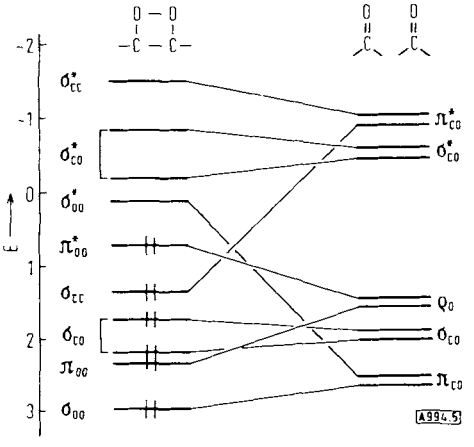


Fig. 5. Orbital correlation diagram depicting the cleavage of a 1,2-dioxetane into two carbonyl fragments (reprinted from [70c]).

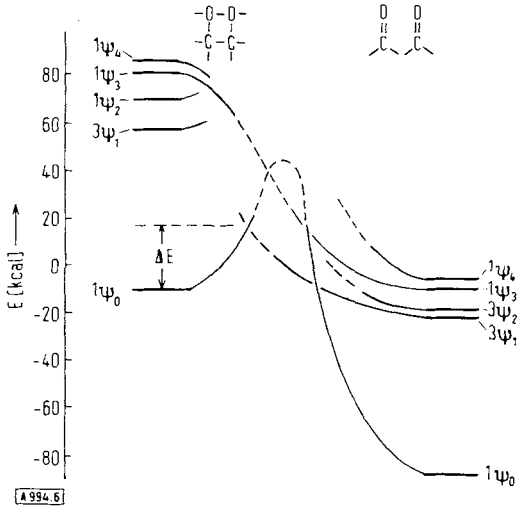


Fig. 6. State correlation diagram depicting the cleavage of a 1,2-dioxetane into two carbonyl fragments (reprinted from [70c]).

Turro and *Lechtken*[71a] have presented further evidence in support of the concerted mechanism. They argue that the biradical mechanism should exhibit four characteristics: an entropy effect, a negative substituent effect, a solvent effect, and a statistical effect. They report that only one criterion is actually observed (the negative substituent effect). Furthermore, they state that the biradical mechanism does not explain the basis for the high yield of triplet states. They propose a pericyclic mechanism in which the transition state becomes asymmetric at some point and thus lowers the prohibition to spin interconversion. In their analysis they apply the formalism of a spin-orbital coupling operator to help rationalize the formation of chemically produced excited states.

Doubt has been cast on their solvent effects recently, however, by *Wilson et al.*[71b]. These authors showed that tetramethyl-1,2-dioxetane decomposes by two competitive paths in meth-

anol and ethanol and that the faster reaction produces no excited states. The rapid "dark" reaction apparently involves an unknown catalyst present in trace amounts. The field of 1,2-dioxetane chemistry continues to be an active one[60, 71c-71f].

3.4. Miscellaneous Methods of Chemiexcitation

In addition to the better known methods of chemiexcitation listed above, a wide variety of methods are available for experimentation. Any reaction that is chemiluminescent can be pressed into service as a source of excited states. A large number of these reactions are covered in various reviews and books on chemiluminescence[3]. Specific mention should be made of the more efficient classes of chemiluminescent compounds such as the hydrazides, the acridine compounds, and the imidazoles. A large number of weakly chemiluminescent compounds were listed in an early article by *Trautz*[72]. No effort has been made in most of the cases to optimize the yields of excited states. This area of research is bound to be a fertile one in the near future.

4. The Transfer of Excitation Energy

4.1. Intermolecular Transfer

Excitation energy can be transferred intermolecularly from an excited donor (D*) to an acceptor (A) to form an excited state of the acceptor molecule (leaving the donor molecule in the ground state) [eq. (1)]. Several mechanisms for intermolecular energy transfer have been proposed. If light is emitted and is then reabsorbed by another molecule, the process is known as radiative energy transfer. Secondly, rigid samples (solids and glasses) may undergo (non-radiative) multiple transfers of excitons[73]. At least two other forms of non-radiative energy transfer can occur in solution[74, 75, 76].

One of these non-radiative processes is operative over only short distances (less than a few angstroms) when the molecules involved are "in contact". In this collisional or exchange mechanism, partial overlap of the electron clouds from two adjacent molecules allows an exchange of electrons, subject to spin selection rules. Collisional exchange has been given a theoretical treatment by *Dexter* and others[77]. An example of this process is the quenching of biacetyl phosphorescence by aromatic hydrocarbons such an anthracene[78]. An alternate explanation for collisional energy transfer reactions in solution involving the formation of a discrete intermediate from the donor and the acceptor has been proposed by *Schenck*[79]. One such intermediate would be a biradical formed during sensitized oxygen transfer[79b]. Further evidence for Schenck intermediates in certain cases has been obtained by *Saltiel*[79d] and by *Turro*[79e].

Resonance or coulombic energy transfer is a second general non-radiative process. Coupling of the oscillating electronic systems of two molecules (corresponding to the coupling of two mechanical oscillators) can result in long-range transfer of energy in solution. The theoretical aspects of resonance energy transfer[80a] have been developed by *Förster*[80b] and discussed by *Bennett* and *Kellogg*[80c]. The efficiency of resonance energy transfer is dependent upon the lifetime of the donor excited state, the distance between the donor and the acceptor, the spins and relative energies of the donor and acceptor states involved in the exchange, and, in some cases, orbital symmetry requirements.

Since energy transfer processes are in competition with other excited state decay mechanisms (emission, quenching), a favorable rate constant is necessary for the observation of energy transfer. The rate may be diffusion controlled for some exchange and resonance transfers[74].

According to current theory[74], resonance energy transfer could occur at separation distances of up to 100 Å. Energy transfer has been observed for distances up to 67 Å[81]. At such distances, multipole interactions greater than dipole-dipole are probably insignificant. For dipole-dipole interactions, the probability of exchange falls off as the inverse sixth power of the separation distance[80b]. Experiments carried out by *Kuhn et al.*[82] using paraffin to maintain a specific distance between monolayers of dyes have resulted in the observation of intermolecular energy transfer.

Energy transfer can occur from either a triplet or a singlet excited state and can produce an excited acceptor of either multiplicity, depending on the system. *Lamola*[76] has pointed out that the efficiency of resonance energy transfer should not be greatly affected by whether the donor transition is allowed or forbidden. Energy transfer has been observed for each of the following cases, where the multiplicities of the excited states are given: singlet-singlet (for example, energy transfer from anthracene to perylene[83a]), triplet-triplet (biacetyl to naphthalene[83b]), triplet-singlet (triphenylamine to chlorophyll a[83c]), and singlet-triplet (perylene to D_{10}-phenanthrene[83d]).

Energy transfer is most efficient when the excited state energy of the donor is nearly the same as the excited state energy of the acceptor. For vertical (Franck-Condon) transitions, overlap between the emission spectrum of the donor and an absorption band of the acceptor favors energy transfer[76]. Non-vertical triplet energy transfer[84] has been suggested to account for transitions that would be endothermic if only spectroscopic states were involved. A non-vertical transition indicates a distortion of molecular geometry to reach an excited state at a minimum energy point (Fig. 7). Proposals describing this distortion include twisting[84a], dissociation[84b], and some degree of bond formation with the donor, possibly in a manner related to the mechanism proposed by *Schenck*[79]. These proposals have been discussed by *Turro*[75] and *Lamola*[76].

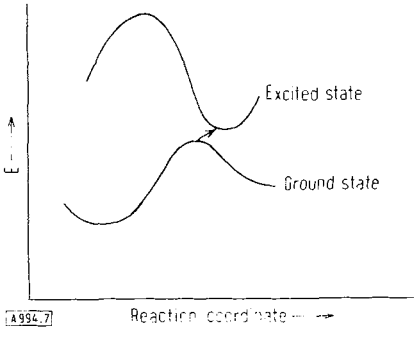


Fig. 7. A non-vertical transition.

Orbital symmetry considerations are thought to be unimportant with respect to most exothermic energy transfers. How-

ever, it has been proposed[85] that when two or more energy transfer processes are in competition, orbital symmetry selection rules may favor population of one excited state over another. This hypothesis was put forward to explain results obtained for the photosensitization of lactones; population of the π,π^* triplet appeared to be favored over the n,π^* triplet, in agreement with orbital correlation diagrams for face-to-face interaction between the sensitizer and acceptor molecules.

4.2. Intramolecular Transfer

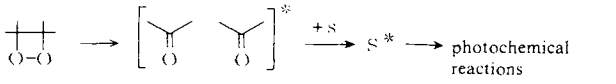
Energy transfer between donor and acceptor moieties in the same molecule has been observed in chromophores including metal chelates[86] such as europium hexafluoroacetylacetonate and in organic molecules, with transfer occurring between such moieties as naphthalene and anthracene[87a]. Intramolecular energy transfer between independent moieties differs from intermolecular transfer only in proximity and orientation effects. The efficiencies of triplet and singlet energy transfer have been measured in some cases[87b] and the rates of energy exchange calculated. Intramolecular energy transfer has recently been observed using the cycloaddition of a norbornylene moiety (acceptor) to a benzene moiety (donor)[87c]. Other workers have studied chromophores in rigid systems[88] in order to determine the effects of distance and orientation on intramolecular energy transfer. Rate data suggest that the exchange mechanism may be operative in some cases[89] while more rigid systems[88c] may involve coulombic or other interactions.

Energy transfer provides a means of producing excited states that are difficult or inconvenient to reach by direct photochemical methods. For example, it can be used to advantage where the absorption band of the molecule of interest overlaps the absorption band of some other component of the system[90a,90b]. Energy transfer introduces the possibility of using chemically produced excited states (rather than photo-produced excited states) in biological[90c] as well as chemical systems (see Section 5).

5. Uses of Chemically Produced Excited States

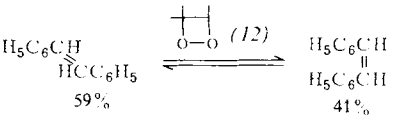
5.1. Chemical Applications

Chemically produced excited states can, of course, undergo "photochemical" changes directly. Precursors could be designed to yield the desired excited state, although with some difficulty. A more useful, and general approach utilizes energy transfer. For example, the decomposition of dioxetanes yields excited states of carbonyl compounds, which under appropriate conditions can transfer the excitation energy to substrates (S), the excited states of which are desired [eq. (32)].



(32)

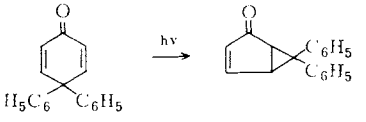
White et al.[4] have used the decomposition of trimethyl-1,2-dioxetane *(12)* to sensitize various reactions, each of which had been extensively studied through the use of photon excitation. In all the cases studied, it appeared that reactions of the triplet state were involved. When either *cis* or *trans* stilbene was heated in benzene with the dioxetane, isomerization was observed and a "photostationary" state was obtained consisting of ≈41% of the *cis* isomer and ≈59% of the *trans* [eq. (33)]. An overall quantum efficiency of about 4% was found for the



(33)

reaction. Quenching with cyclooctatetraene resulted in a drastic reduction of the apparent quantum yield, (0.04%) and in general, low dioxetane concentrations and high stilbene concentrations increased the apparent quantum yield.

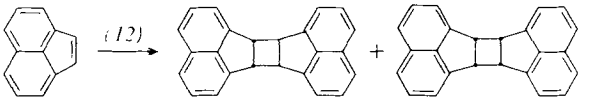
The principle of "photochemistry without light" was also applied to the photoisomerism of 4,4-diphenylcyclohexadienone [eq. (34)][4a,4b].



(34)

The apparent quantum yield of this reaction was 0.4%. The triplet state of the dienone (involved in the rearrangement) was reported to be 69 kcal/mol[91]; thus quanta of approximately this energy are available from the decomposition of trimethyl-1,2-dioxetane.

The dimerization of acenaphthylene *(13)* using trimethyl-1,2-dioxetane *(12)* as a chemical sensitizer was also reported [eq. (35)][4b]. Both *cis* and *trans* isomers were formed, the



(13)

(35)

ratio suggesting that triplet excited states were involved. The reaction was strongly quenched by cyclooctatetraene, as expected.

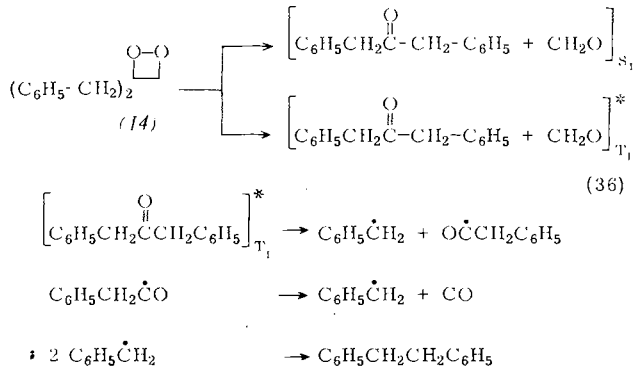
The usefulness of the concept of photochemistry through chemically produced excited states is exemplified by the following simple procedure. A solution of the dioxetane and acenaphthylene is heated in steam for about ten minutes; on cooling, crystals of the *trans* dimer separate. The apparent quantum yield is a simple function of the chemical yield.

In addition to the above transformation, trimethyl-1,2-dioxetane has also been used to sensitize the conversion of santonin to lumisantonin (see Section 5.2).

Richardson et al.[92] have shown that the thermal decomposition of 3,3-dibenzyl-1,2-dioxetane *(14)* produces bibenzyl and dibenzyl ketone in 2.2% and 88% yield, respectively.

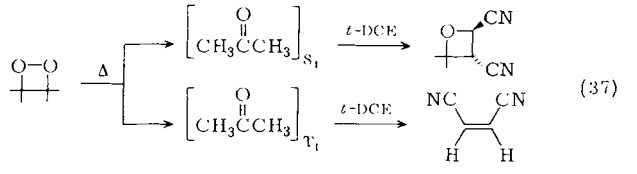
Bibenzyl is presumably formed from triplet dibenzyl ketone in a Norrish Type I process [eq. (36)].

In another interesting example of the use of chemically produced excited states, *Turro* and *Lechtken*[62] have "titrated" the excited states from the decomposition of tetramethyl-1,2-dioxetane with dicyanoethylene. The reaction of excited singlet



(36)

and triplet acetone with *trans*-1,2-dicyanoethylene (*t*-DCE) produced two different products [eq. (37)]. These authors

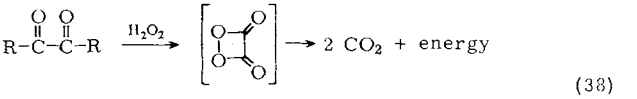


(37)

have also reported that tetramethyldioxetane sensitized the conversion of 1,2-diethoxyethylene from the *cis* to the *trans* form and that thermolysis of the dioxetane in the presence of norbornene produced norbornene dimers.

White and *Wildes*[4d] have used chemically produced excited states and energy transfer to produce chemiluminescence. They used trimethyl-1,2-dioxetane to sensitize the fluorescence of lanthanide chelates in solution. When 1,10-phenanthroline-tris[1-(2-thienyl)-4,4,4-trifluoro-1,3-butanedionato]europium-(III) was used as the fluorescent acceptor, at least 80% of the light emitted appeared in a band having a total width of 5 nm. This very narrow band emission allows the system to be used as a chemical source of "monochromatic" light devised to generate a specific number of photons.

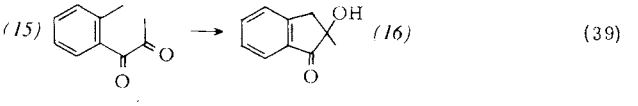
Güsten and *Ullman*[93] have performed "photochemistry without light" using oxalic acid derivatives and hydrogen peroxide to sensitize the reactions. It has been proposed that the oxalate-hydrogen peroxide reactions yield 1,2-dioxetanedione, which subsequently decomposes to give excited products [eq.



(38)

R = 2,4-$(NO_2)_2C_6H_3O$ or 2,4,6-$Cl_3C_6H_2O$

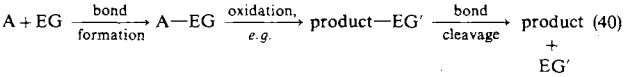
(38)][47]. They have used this method to transform 1-(*o*-tolyl)-1,2-propanedione *(15)* to the known photoproduct, 2-hydroxy-2-methylindanone *(16)* [eq. (39)].



(39)

A chemical sensitization efficiency of 0.006 was reported for the reaction. They have also used this method to convert phenanthraquinone and ethyl vinyl ether to the known photoadduct and have converted *trans*-4-methoxy-4'-nitrostilbene to the *cis* form with a chemical sensitization efficiency of 0.045.

All of the above examples of the uses of chemically produced excited states utilize intermolecular energy transfer. In situations where only low concentrations of reactants are desirable, intramolecular energy transfer may be an answer. One can generalize this approach: intramolecular energy transfer from one of the energy generators (EG) used in chemiluminescence to an acceptor molecule (A) attached by a labile bond to the energy generator [eq. (40)][4a].



(40)

5.2. Possible Biological Uses

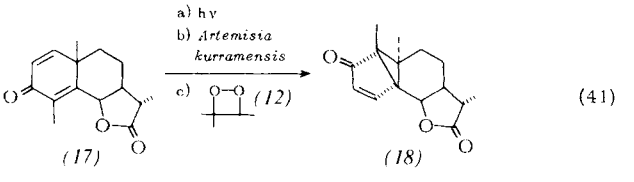
A large number of living organisms are known to produce electronically excited states[94a]; light emission from these chemically produced excited states occurs in the bioluminescence of organisms such as the firefly (Fig. 2, paths 1 and 3). Since chemically produced excited states have been shown to undergo "photochemical" changes in addition to light emission (Section 5.1), it appears reasonable to assume that both pathways will also be available to biochemically produced excited states. That is, chemically produced excited states may be playing a chemical role in biological systems[4c, 94b].

Biochemically produced excited states will presumably be found operating in dark (non-photochemical) reactions that appear, superficially, to be photochemical reactions. Several criteria must be satisfied for a convincing demonstration of the occurrence of "photobiology without light": (1) the organism should contain two or more compounds (A, B,...) that are related by the action of light *in vitro* (A + hν → B); (2) the compounds A and B must not be interconvertible in ground state reactions; (3) the organism (or enzyme system) must be able to convert A into B in the absence of light.

Since the rigor of criterion 2 is dependent on the state of the art and since enzymes might be able to catalyze ground and excited state reactions unknown to the synthetic chemist, additional criteria would be desirable: *e.g.*, the pathways for the biosynthesis of A and B should be known, and the conversion of A into B should be demonstrable with isolated enzyme systems. We will now summarize our preliminary work in this area and list cases where it seems *possible* that biochemically produced excited states are involved in biochemical transformations.

5.2.1. Simple Chemical Conversions

The first example concerns a pair of compounds found in various species of *Artemisia*[95,96]: the sesquiterpene lactone, santonin *(17)* and its photoisomer, lumisantonin *(18)* [eq. (41)] (which is readily made from *(17)* by the action of light).



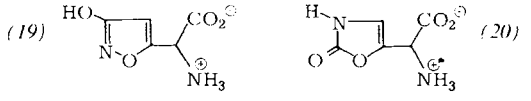
(41)

White and *Wei*[4c] have recently employed chemically produced excited states in a biogenetic type transformation of santonin to lumisantonin. The excited states resulting from thermolysis of trimethyldioxetanes were used to sensitize the reaction [eq. (41c)]. Investigation of the *in vivo* conversion in *Artemisia kurramensis* indicates, however, that at least part of the reaction is photochemical[97]. Surprisingly, examples of simple photobiological transformations such as the santonin-lumisantonin conversion are not very numerous. One other example has been well documented by *Haskins, Gorz*, and *Williams*; these authors found that the conversion of *trans* to *cis*-β-D-glucosyl-*o*-hydroxycinnamic acid in *Melilotus alba* was sunlight mediated [eq. (42)][98].



(42)

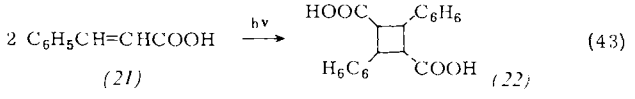
In their communication, *White* and *Wei* enumerated several other cases where a natural product and its photochemical conversion products have been isolated from the same species[4c]. It was noted that *Eugster et al.*[99] isolated both ibotenic acid *(19)* and muscazone *(20)* from various species of the



(19) *(20)*

mushroom *Amanita*. Ibotenic acid can be photochemically converted to muscazone *in vitro*; *Eugster* estimated that the amount of light available to the mushroom was insufficient for the *in vivo* conversion, however. One possible alternative would involve a photoisomerization sensitized by an enzymatically generated excited state.

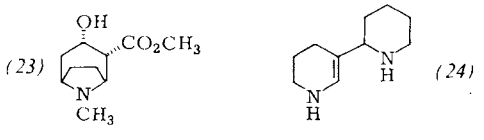
The biosynthesis of cyclobutanes is another biological process which may involve the use of chemically generated excited states. Cyclobutanes can be readily made by the photochemical dimerization of alkenes [*e.g.* eq. (43)]. Both cinnamic acid *(21)* and truxillic acid *(22)* derivatives have been isolated



(43)

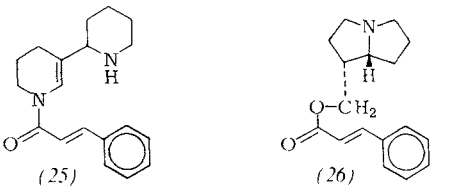
(21) *(22)*

from various organisms. *Liebermann*[100] and *Hesse*[101] independently isolated truxillic and truxinic acids following acid hydrolysis of the leaves of *Erythroxylon coca*. The dimers occur in the plant as the truxillates and truxinates of (−)-ecgonine methyl ester *(23)*. The cinnamoyl monomer was also isolated from the same plant.



(23) *(24)*

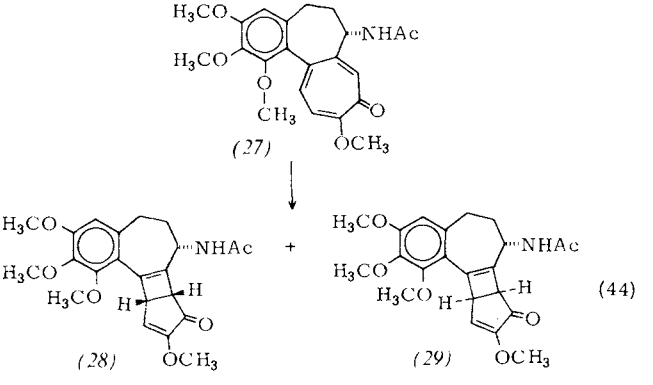
Another naturally occurring alkaloid derivative of α-truxillic acid *(22)* is santiaguine, isolated from *Adenocarpus* species[102]. Santiaguine is the diamide of α-truxillic acid and 1,4,5,6-tetrahydroanabasine *(24)*. It has recently been shown



(25) *(26)*

by ^{14}C labeling studies that the cinnamoyl monomer orensine *(25)*[*], is a precursor of santiaguine in *Adenocarpus foliosus*[103]. Similarly, thesinine *(26)* and its cyclobutane dimer, thesine, have been isolated from *Thesium minkwitzianum*[104]. The most recently reported truxillic acid derivative is gratissimin, which is the dimethyl ester of α-truxillic acid[105]. The biosynthesis of other cyclobutanes such as α- and β-pinene and caryophyllene may also occur *via* the intermediacy of biochemically generated excited states.

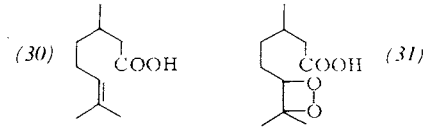
The conversion of colchicine *(27)* into the lumicolchicines *(28)* and *(29)* [eq. (44)] is another reaction in which biochemically generated excited states may be involved. Colchicine and both β- and γ-lumicolchicine [*(28)* and *(29)* respectively] have been isolated from *Colchicum autumnale* and furthermore, colchicine can be converted into the lumicolchicines *in vitro* with light[106].



(27)

(28) *(29)* (44)

Lamola has used the electronically excited states derived from the decomposition of trimethyldioxetane *(12)* to dimerize pyrimidine residues in *E. coli* DNA[107]. The analogous photochemical dimerization of pyrimidine bases is responsible for the lethal effects of short wavelength UV light on organisms[108]. It is interesting in this connection, but disappointing, that trimethyldioxetane, 4-*n*-butyl-3,3-dimethyldioxetane and the 1,2-dioxetane analog *(31)* of the naturally occurring monoterpene, citronellic acid *(30)*, showed no activity in tests for mutagenicity with the bacteria *Salmonella typhimurium*[109].



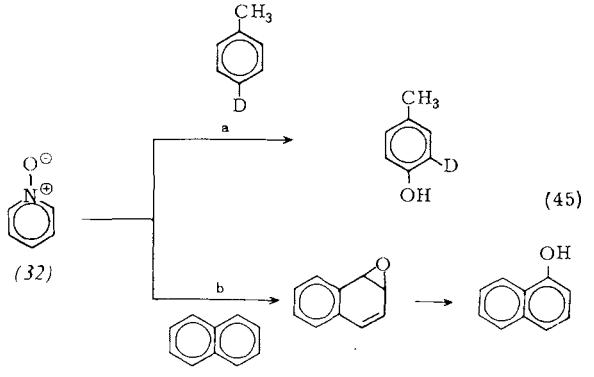
(30) *(31)*

It has been shown that organisms can repair photochemically damaged DNA by an enzyme-catalyzed light-dependent monomerization of the cyclobutane pyrimidine dimers. *Cook*[110] has examined the phylogenetic distribution of the photoreactivating enzyme and has found the photorepair activity occur-

[*] Called "adenocarpine" for the optically active form; Ref. [103].

ring in nocturnal animals (*e.g.*, adult land crab) and in tissue shielded from external radiation (*e.g.*, opossum liver)[111]. The occurrence of photoreactivating enzyme activity in tissue where no light is available (under normal circumstances) is an indication that the excited states needed for the monomerization may be generated chemically. In this connection, however, *Cook* and *Setlow* have both been unsuccessful in their attempts to demonstrate under conditions of darkness the repair of photodamaged DNA using cell extracts known to contain photoreactivating activity[111].

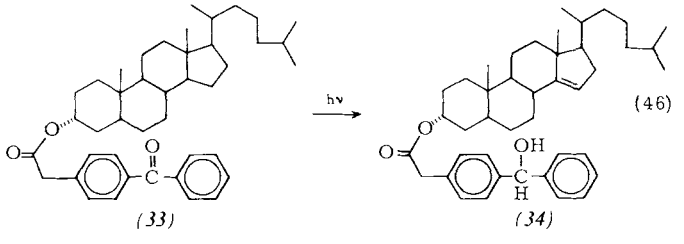
Recently *Jerina*, *Boyd*, and *Daly*[112] have devised a photochemical model for enzymic oxygenations. These workers proposed that a photochemical oxygen atom transfer from pyridine-*N*-oxide *(32)* was a model for enzymatic oxygenations in that it fulfilled the requirements of hydroxylation (eq. (45), paths a and b), NIH shift[*] (path a) and epoxidation (path



(32) (45)

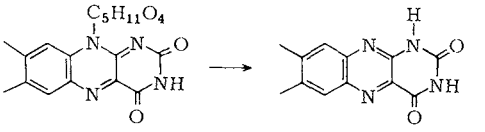
b). Theoretical support of the photochemical model was provided by *Kumaki et al.*[113], who found that the position of enzymic hydroxylation of aromatic compounds is in agreement with calculated parameters for a nucleophilic attack on the first electronic excited state. It is possible that biochemically produced excited states may be involved in the *in vivo* process.

Another photochemical model for a biological process has recently been reported by *Breslow*[114]. It was found that a properly oriented benzophenone triplet could mimic the ability of certain enzymes to oxidize unactivated methylene groups. For example, the photolysis of the benzophenone-4-acetyl ester of 3α-cholestanol *(33)* led to the 14-alkene [*(34)*, eq. (46)].



(33) *(34)* (46)

Other biosyntheses which may involve chemically generated electronically excited states are[4d]: 1) the bioformation of lumichrome [eq. (47)], a compound synthesized *in vitro* by the irradiation of riboflavin[115]; and 2) the biogenesis of vitamin D in fish. In the latter case, *Bills* found that neither sunlight nor the food ingested could account for the quantities of vitamin D in cod or catfish[116]. Further, it has been pointed



(47)

out that the amount of vitamin D in the black-backed flounder exceeds the amount that could be formed in a purely photochemical pathway by the total light absorbed by the flounder[117]. In this connection, *Blondin*, *Kulkarni*, and *Nes* have shown that vitamin D can be synthesized from dehydrocholesterol by fish liver homogenates incubated in the dark[118].

Chemically generated excited states may also be involved in the dark regeneration of the biological clock pigment, phytochrome, from the far-red absorbing form[119] and in the dark regeneration of 11-*trans*-retinal from the *cis* form in the visual process[120]. Lastly, the photoactivation of enzymes such as urocanase should be examined in the context of biochemically produced excited states[121].

Chemically produced excited states have been specifically invoked in two instances recently. *Pettus* and *Moore* suggested that biochemically generated excited states may be involved in the biosynthesis of dictyopterene B *(36)* in the algae *Dictyopteris*[122]. The authors noted that the cyclopropane ring of dictyopterene B "may be formed by an enzymatically controlled and photochemically induced (with or without light) di-π-methane rearrangement" of a fatty acid homolog of *(35)*.



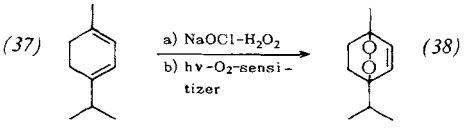
(35) *(36)* (48)

Buu-Hoï and *Sung* have proposed that biochemically generated electronic excited states may be involved in the carcinogenic activity of polynuclear aromatic hydrocarbons[123]. It has been shown that aromatic hydrocarbons combine with DNA under photochemical conditions[124]; further, *Santamaria et al.* have demonstrated that light enhanced the carcinogenicity of the polynuclear aromatic hydrocarbon benzopyrene in mice[125]. The suggestion of *Buu-Hoï* and *Sung* then is that the carcinogenic aromatic hydrocarbons are converted to their electronically excited states and that these react with cellular substrates such as proteins and DNA.

5.2.2. Singlet Oxygen

Oxygen in its electronically excited singlet state has been generated chemically from superoxide ion[126a] and from hydrogen peroxide[126b] (see also Ref. [16c]).

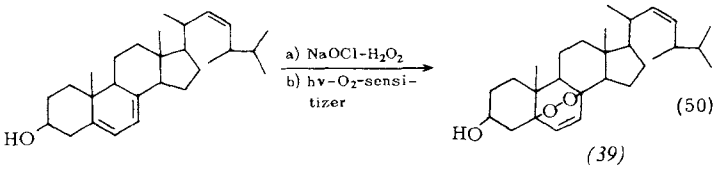
The oxidation of hydrogen peroxide by hypochlorite resulted in the formation of excited singlet oxygen which gave the same products as photochemically generated singlet oxygen.



(37) *(38)* (49)

[*] The effect whereby substituents on benzene rings are displaced to a neighboring position by the incoming hydroxy group in enzymic oxygen transfers has been named by its discoverers as "NIH shift", after their place of work (National Institutes of Health).

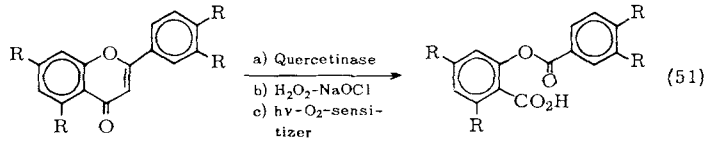
For example α-terpinine *(37)* yielded the endoperoxide ascaridole [*(38)*, eq. (49)], which is the chief constituent of the oil of *Chenopodium*[127]. Similarly, the endoperoxide of ergosterol was formed both by photooxygenation and by reaction with chemically generated singlet oxygen [eq. (50)][126b]. The



(39)

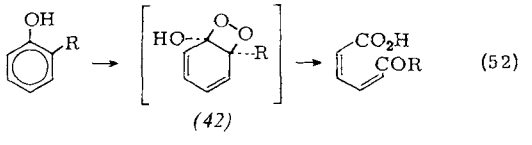
endoperoxide of ergosterol *(39)* is especially interesting because it has been isolated from a mold grown in the dark[128]; analogous dehydrocholesterol endoperoxides have been isolated from mammalian liver[129].

Matsuura et al.[130] have used the hypochlorite-peroxide reaction as a model for the dioxygenase, quercetinase, which converts the flavone quercetin *(40)* to acid *(41)* [eq. (51)].



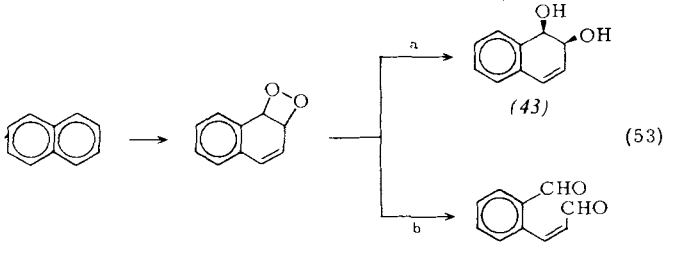
(40) *(41)*

Singlet oxygen has also been implicated in the cleavage of aromatic nuclei by dioxygenases[131]. The reaction is thought to proceed *via* a dioxetane intermediate [*(42)*, eq. (52)][131].



(42)

Analogous dioxetane intermediates have been postulated in the chemiluminescence of polyacene endoperoxides[132]. Evidence for the *in vivo* intermediacy of the dioxetane originates from the isolation and identification of *cis*-1,2-dihydro-1,2-naphthalenediol *(43)* from several strains of bacteria[133]. It should be pointed out that the decomposition of the dioxetane [eq. (53), path b] could lead to the generation of useful excited states. *Cis*-diols similar to *(43)* have been isolated in the microbial metabolism of benzene[134] and benzoic acid[135], and analogous dioxetane precursors have been proposed.



(43)

Recently, *Allen et al.* observed chemiluminescence from human polymorphonuclear leucocytes during phagocytosis[136]. They proposed that the bactericidal activity of polymorphonuclear leucocytes was due to chemically generated singlet oxygen. In addition, *Chan* has detected singlet-like oxygenation activity in enzyme systems[137, 138]. Horseradish peroxidase was found to convert 1,3-diphenylisobenzofuran to *o*-dibenzoylbenzene, the product observed from photosensitized oxygenation of the parent furan[137]. Similarly, the oxygenation of 1,3-dienes by soybean lipoxidase was reported[138]. Other examples of the involvement of singlet oxygen in biological systems have recently been reviewed[139].

5.2.3. Complex Cases

It would be interesting to see whether chemically produced excited states can be used to replace some or all of the light required for complex photobiological processes such as photosynthesis, phototaxis, photoperiodism (*e. g.*, action on the pineal gland), and visual processes. In preliminary work, we have been unable to initiate "light" dependent chlorophyll synthesis in dark grown *Euglena* with trimethyl-1,2-dioxetane and with 4-*n*-butyl-3,3-dimethyl-1,2-dioxetane[140]. In addition, trimethyl-1,2-dioxetane applied to one side of an etiolated oat seedling did not give a "phototropic" response in darkness[141].

Lastly, generators of electronically excited states such as the dioxetanes may provide a unique mode of drug action since they can deliver excited states to internal organs that are normally inaccessible to light.

6. Conclusion

Chemically generated excited states can be produced efficiently, and utilized to drive "photochemical" reactions. The technique can be useful in that the procedures are simple, simple apparatus is sufficient, and apparent quantum yields can be determined from yield data. In bifunctional molecules used for energy transfer studies, only the chemical method of excitation insures that all the excitation energy resides initially in the donor portion of the molecule; this factor can be important when there is considerable overlap between the absorption spectra of the donor and acceptor. Finally, studies of chemically produced excited states will yield background information which may lead to the discovery of like phenomena in biological systems[*].

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[*] After this manuscript had been accepted for publication, we learned that a review entitled "Excited Electronic States in Dark Biological Reactions" by *G. Cilento* will be published in Quarterly Reviews of Biophysics.

[1] *W. D. McElroy* and *B. Glass*: Light and Life. The Johns Hopkins Press, Baltimore, 1961.

[2] *H. H. Jaffé* and *M. Orchin*: Theory and Applications of Ultraviolet Spectroscopy. Wiley, New York 1962.

[3] a) *K. D. Gundermann*: Chemilumineszenz Organischer Verbindungen. Springer, Berlin 1968; Angew. Chem. 77, 572 (1965); Angew. Chem. internat. Edit. 4, 566 (1965); b) *E. H. White* and *D. F. Roswell*, Accounts Chem. Res. 3, 54 (1970); c) *F. McCapra*, Pure Appl. Chem. 24, 611 (1970).

[4] a) *E. H. White, J. Wiecko*, and *D. F. Roswell*, J. Amer. Chem. Soc. 91, 5194 (1969); b) *E. H. White, J. Wiecko*, and *C. C. Wei, ibid.* 92, 2167 (1970); c) *E. H. White* and *C. C. Wei*, Biochem. Biophys. Res. Commun. 39, 1219 (1970); d) *P. D. Wildes* and *E. H. White*, J. Amer. Chem. Soc. 93, 6286 (1971).

[5] *J. G. Calvert* and *J. N. Pitts, Jr.*: Photochemistry. Wiley, New York 1966; *R. O. Kan*: Organic Photochemistry. McGraw-Hill, New York 1966; *N. J. Turro*: Molecular Photochemistry. Benjamin, New York 1965.

[6] *R. Audubert*, Trans. Faraday Soc. *35*, 197 (1939).

[7] *S. G. Entelis, V. Ya. Shlyapintokh, O. N. Karpukhin*, and *O. V. Nesterov*, Zh. Fiz. Khim. *34*, 1651 (1960).

[8] *E. H. White*, J. Chem. Educ. *34*, 275 (1957).

[9] Incandescent bulbs are about 3% efficient (see, *e.g., J. O. Kraehenbuehl*: Electrical Illumination. Wiley, New York 1947, p. 123).

[10] *H. H. Seliger* and *W. D. McElroy*, Biochem. Biophys. Res. Commun. *1*, 21 (1959); Arch. Biochem. Biophys. *88*, 136 (1960).

[11] *O. Shimomura* and *F. H. Johnson*, Photochem. Photobiol. *12*, 291 (1970).

[12] *J. Lee*, Biochemistry *11*, 3350 (1972).

[13] *M. M. Rauhut, L. J. Bollyky, B. G. Roberts, M. Loy, R. H. Whitman, A. V. Iannotta, A. M. Semsel*, and *R. A. Clarke*, J. Amer. Chem. Soc. *89*, 6515 (1967).

[14] *R. B. Brundrett, D. F. Roswell*, and *E. H. White*, J. Amer. Chem. Soc. *94*, 7536 (1972).

[15] a) *C. C. Wei* and *E. H. White*, Tetrahedron Lett. *1971*, 3559; b) The values involve corrections for various quenching processes (*T. Wilson* and *A. P. Schaap*, J. Amer. Chem. Soc. *93*, 4126 (1971); *N. J. Turro* and *P. Lechtken*, *ibid 94*, 2886 (1972); *D. J. Freed* and *L. R. Faulkner*, *ibid. 94*, 4790 (1972).

[16] a) *R. C. Dougherty*, J. Amer. Chem. Soc. *93*, 7187 (1972); b) *J. A. Howard* and *K. U. Ingold*, *ibid. 90*, 1056 (1968); c) It should be noted in this connection that excited singlet states of oxygen, a molecule with a triplet ground state, are readily formed in a variety of non-radical reactions of singlet reactants (*A. C. Giese*: "Photophysiology". Academic Press, New York 1970. Vol. V, Chapters 2 and 3). d) The formation of thermally formed triplet states of charge-transfer complexes has been claimed [see *e.g. R. T. Keys* and *W. R. Carper*, J. Chem. Phys. *47*, 3682 (1967)]; it appears possible, however, that the observations may have been due to impurities that were strong reducing agents.

[17] a) *B. A. Thrush*, Chem. Brit. *2*, 287 (1966); b) *K. H. Becker* and *K. D. Bayes*, J. Chem. Phys. *45*, 396 (1966); c) *J. L. Gole* and *R. N. Zare*, *ibid. 57*, 5331 (1972).

[18] *P. N. Clough, S. E. Schwartz*, and *B. A. Thrush*, Proc. Roy. Soc. (London) *A 317*, 575 (1970).

[19] *M. C. Lin* in *M. J. Cormier, D. M. Hercules*, and *J. Lee*: Chemiluminescence and Bioluminescence. Plenum Press, New York 1973, p. 61.

[20] *J. S. Arnold, R. J. Broune*, and *E. A. Ogryzlo*, Photochem. Photobiol. *4*, 963 (1965).

[21] *A. U. Khan* and *M. Kasha*, J. Amer. Chem. Soc. *88*, 1574 (1966).

[22] *R. B. Kurtz*, Trans. N. Y. Acad. Sci. *16*, 399 (1954).

[23] *F. Kaufman* in *M. J. Cormier, D. M. Hercules*, and *J. Lee*: Chemiluminescence and Bioluminescence. Plenum Press, New York 1973, p. 83.

[24] *A. Fontijn, C. B. Meyer*, and *H. I. Schiff*, J. Chem. Phys. *40*, 64 (1964).

[25] *A. Fontijn* and *J. Lee*, J. Opt. Soc. Amer. *62*, 1095 (1972).

[26] *F. Kaufman*, J. Chem. Phys. *28*, 352 (1958); *P. Harteck, R. R. Reeves*, and *G. Mannella*, *ibid. 29*, 1333 (1958).

[27] *A. Zweig*, Advan. Photochem. *6*, 425 (1968).

[28] *D. M. Hercules*, Accounts Chem. Res. *2*, 301 (1969).

[29] *R. E. Visco* and *E. A. Chandross*, J. Amer. Chem. Soc. *86*, 5350 (1964).

[30] *A. Weller* and *K. Zachariasse* in *M. J. Cormier, D. M. Hercules*, and *J. Lee*: Chemiluminescence and Bioluminescence. Plenum Press, New York 1973, pp. 169, 181.

[31] *D. L. Maricle, A. Zweig, A. H. Maurer*, and *J. S. Brinen*, Electrochim. Acta *13*, 1209 (1968).

[32] a) *E. A. Chandross* and *F. I. Sonntag*, J. Amer. Chem. Soc. *88*, 1089 (1966); b) *O. C. Zafiriou*, unpublished work.

[33] *R. A. Marcus*, J. Chem. Phys. *43*, 2654 (1965); *52*, 2803 (1970); Electrochim. Acta *13*, 995 (1968).

[34] *A. Zweig, A. K. Hoffmann, D. L. Maricle*, and *A. H. Maurer*, J. Amer. Chem. Soc. *90*, 261 (1968).

[35] *D. J. Freed* and *L. R. Faulkner*, J. Amer. Chem. Soc. *93*, 2097 (1971).

[36] *G. Briegleb, W. Herre, W. Jung*, and *H. Schuster*, Z. Phys. Chem. N. F. *45*, 229 (1965).

[37] a) *E. S. Pysh* and *N. C. Yang*, J. Amer. Chem. Soc. *85*, 2124 (1963); b) *K. S. V. Santhanam* and *A. J. Bard*, *ibid. 87*, 139 (1965); c) *A. Weller* and *K. Zachariasse*, J. Chem. Phys. *46*, 4984 (1967); d) *D. M. Hercules, R. C. Lansbury*, and *D. K. Roe*, J. Amer. Chem. Soc. *88*, 4578 (1966); e) *J. Chang, D. M. Hercules*, and *D. K. Roe*, Electrochim. Acta *13*, 1197 (1968); f) *G. J. Hoytink*, Discuss. Faraday Soc. *45*, 14 (1968).

[38] *C. A. Parker* and *C. G. Hatchard*, J. Phys. Chem. *66*, 2506 (1962).

[39] *A. Weller* and *K. Zachariasse*, Chem. Phys. Lett. *10*, 197 (1971).

[40] a) *E. A. Chandross, J. W. Longworth*, and *R. E. Visco*, J. Amer. Chem. Soc. *87*, 3259 (1965); b) *E. A. Chandross* and *F. I. Sonntag*, *ibid. 88*, 1089 (1966).

[41] *D. M. Hercules* in *A. Weissberger* and *B. W. Rossiter*: Techniques of Chemistry. Vol. I, Part IIB. Wiley-Interscience, New York 1971, pp. 257–344.

[42] *D. L. Maricle* and *A. Maurer*, J. Amer. Chem. Soc. *89*, 188 (1967).

[43] *A. J. Bard, C. P. Keszthelyi, H. Tachikawa*, and *N. E. Tokel* in *M. J. Cormier, D. M. Hercules*, and *J. Lee*: Chemiluminescence and Bioluminescence. Plenum Press, New York 1973, p. 193.

[44] a) *E. H. White* and *M. J. C. Harding*, J. Amer. Chem. Soc. *86*, 5686 (1964); b) *E. H. White* and *M. J. C. Harding*, Photochem. Photobiol. *4*, 1129 (1965).

[45] *F. McCapra* and *Y. C. Chang*, Chem. Commun. *1966*, 522.

[46] *F. McCapra, D. G. Richardson*, and *Y. C. Chang*, Photochem. Photobiol. *4*, 1111 (1965).

[47] *M. M. Rauhut*, Accounts Chem. Res. *2*, 80 (1969).

[48] a) *W. H. Urry* and *J. Sheeto*, Photochem. Photobiol. *4*, 1067 (1965); b) *W. Carpenter* and *E. M. Bens*, Tetrahedron *26*, 59 (1970).

[49] *E. H. White, E. Rapaport, H. H. Seliger*, and *T. A. Hopkins*, Bioorganic Chem. *1*, 92 (1971).

[50] *T. Goto* and *Y. Kishi*, Angew. Chem. *80*, 417 (1968); Angew. Chem. internat. Edit. *7*, 407 (1968).

[51] *K. R. Kopecky* and *C. Mumford*, Can. J. Chem. *47*, 709 (1969).

[52] *K. R. Kopecky, J. H. Van de Sande*, and *C. Mumford*, Can. J. Chem. *46*, 25 (1968).

[53] a) P. D. Bartlett and *A. P. Schaap*, J. Amer. Chem. Soc. *92*, 3223 (1970); b) *P. D. Bartlett, G. D. Mendenhall*, and *A. P. Schaap*, Ann. N. Y. Acad. Sci. *171*, 79 (1970); c) *A. P. Schaap*, Tetrahedron Lett. *1971*, 1757; d) *T. Wilson* and *A. P. Schaap*, J. Amer. Chem. Soc. *93*, 4126 (1971).

[54] *S. Mazur* and *C. S. Foote*, J. Amer. Chem. Soc. *92*, 3225 (1970).

[55] *A. P. Schaap* and *P. D. Bartlett*, J. Amer. Chem. Soc. *92*, 6055 (1970).

[56] *J. H. Wieringa, J. Strating, H. Wynberg*, and *W. Adam*, Tetrahedron Lett. *1972*, 169.

[57] *P. R. Story, E. A. Whited*, and *J. A. Alford*, J. Amer. Chem. Soc. *94*, 2143 (1972).

[58] a) *H. Staudinger*, Ber. Deut. Chem. Ges. *58*, 1088 (1925); b) *P. S. Bailey*, Chem. Rev. *58*, 925 (1958).

[59] *N. C. Yang* and *R. V. Carr*, Tetrahedron Lett. *1972*, 5143.

[60] *K. R. Kopecky, P. A. Lockwood, J. E. Filby*, and *R. W. Reid*, Can. J. Chem. *51*, 468 (1973); we thank Professor *Kopecky* for a preprint of this paper. In this connection, we have been unable to reproduce the synthesis of the dioxetane of bifluorenylidine by the ozone approach [59].

[61] a) *W. Adam* and *J-C. Liu*, J. Amer. Chem. Soc. *94*, 2894 (1972); b) *W. Adam* and *H.-C. Steinmetzer*, Angew. Chem. *84*, 590 (1972); Angew. Chem. internat. Edit. *11*, 540 (1972).

[62] *N. J. Turro* and *P. Lechtken*, J. Amer. Chem. Soc. *94*, 2886 (1972).

[63] *W. H. Richardson, M. B. Yelvington*, and *H. E. O'Neal*, J. Amer. Chem. Soc. *94*, 1619 (1972).

[64] a) *H. E. O'Neal* and *W. H. Richardson, J. Amer. Chem. Soc. 92*, 6553 (1970); b) *W. H. Richardson* and *H. E. O'Neal*, *ibid. 94*, 8665 (1972).

[65] a) *R. F. Borkman* and *D. R. Kearns*, J. Chem. Phys. *44*, 945 (1966); b) *J. C. D. Brand*, J. Chem. Soc. *1956*, 858.

[66] *H. E. O'Neal* and *W. H. Richardson*, J. Amer. Chem. Soc. *93*, 1828 (1971).

[67] *L. J. Bollyky*, J. Amer. Chem. Soc. *92*, 3230 (1970).

[68] *F. McCapra*, Chem. Commun. *1968*, 155.

[69] a) *R. B. Woodward* and *R. Hoffmann*, Angew. Chem. *81*, 797 (1969); Angew. Chem. internat. Edit. *8*, 781 (1969).

[70] a) *D. R. Kearns* and *A. U. Khan*, Photochem. Photobiol. *10*, 193 (1969); b) *D. R. Kearns*, J. Amer. Chem. Soc. *91*, 6554 (1969); c) Chem. Rev. *71*, 395 (1971).

[71] a) *N. J. Turro* and *P. Lechtken*, J. Amer. Chem. Soc. *95*, 264 (1973); b) *T. Wilson, M. E. Landis, A. L. Baumstark*, and *P. D. Bartlett*, *ibid. 95*, 4765 (1973); c) *P. D. Bartlett, A. L. Baumstark*, and *M. E. Landis*, *ibid. 95*, 6486 (1973); d) *N. J. Turro, P. Lechtken, A. Lyons, R. R. Hautala, E. Carnahan*, and *T. J. Katz*, *ibid. 95*, 2035 (1973); e) *P. Lechtken, A. Yekta*, and *N. J. Turro*, *ibid. 95*, 3027 (1973); f) *N. J. Turro, H.-C. Steinmetzer*, and *A. Yekta*, *ibid. 95*, 6468 (1973).

[72] *M. Trautz*, Z. Phys. Chem. *53*, 1 (1905).

[73] a) *A. S. Davydov*: Theory of Molecular Excitons. McGraw-Hill, New York 1962; b) *V. L. Ermolaev*, Sov. Phys. Usp. *6*, 333 (1963).

[74] *F. Wilkinson*, Advan. Photochem. *3*, 241 (1964).

[75] *N. J. Turro, J. C. Dalton*, and *D. S. Weiss* in *O. L. Chapman*: Organic Photochemistry. Vol. 2. Marcel Dekker, New York 1969, pp. 1ff.

[76] *A. A. Lamola* in *P. A. Leermakers* and *A. Weissberger*: Techniques of Organic Chemistry. Vol. XIV. Interscience, New York 1969, pp. 17ff.

[77] a) *D. L. Dexter*, J. Chem. Phys. *21*, 836 (1953); b) *M. Inokuti* and *F. Hirayama*, *ibid. 43*, 1978 (1965).

[78] *H. L. J. Bäckström* and *K. Sandros*, Acta Chem. Scand. *12*, 823 (1958).

[79] a) *G. O. Schenck* and *R. Steinmetz*, Bull. Soc. Chim. Belg. *71*, 781 (1962); b) *K. Gollnick* and *G. O. Schenck*, Pure Appl. Chem. 9, 507 (1964); c) *N. C. Yang*, *J. I. Cohen*, and *A. Shani*, J. Amer. Chem. Soc. 90, 3264 (1968); d) *J. Saltiel*, *K. R. Neuberger*, and *M. Wrighton*, *ibid. 91*, 3658 (1969); e) *N. J. Turro* and *P. A. Wriede*, *ibid. 92*, 320 (1970).

[80] a) *J. Perrin*, C.R. Acad. Sci. *184*, 1097 (1927); b) *T. Förster*, Discuss. Faraday Soc. *27*, 7 (1959); c) *R. G. Bennett* and *R. E. Kellogg*, Progr. React. Kinet. *4*, 215 (1967).

[81] *W. R. Ware*, J. Amer. Chem. Soc. *83*, 4374 (1961).

[82] a) *M. M. Zwick* and *H. Kuhn*, Z. Naturforsch. *17A*, 411 (1962); b) *K. H. Drexhage*, *M. M. Zwick*, and *H. Kuhn*, Ber. Bunsenges. Phys. Chem. 67, 62 (1963); *H. Kuhn* and *D. Möbius*, Angew. Chem. *83*, 672 (1971); Angew. Chem. internat. Edit. *10*, 620 (1971).

[83] a) *W. R. Ware*, J. Phys. Chem. *66*, 455 (1962); b) *G. Porter* and *F. Wilkinson*, Proc. Roy. Soc. *A264*, 1 (1961); c) *V. L. Ermolaev* and *E. B. Sveshnikova*, Bull. Acad. Sci. USSR, Phys. Ser. *26*, 29 (1962); d) *R. G. Bennett*, J. Chem. Phys. *41*, 3048 (1964).

[84] a) *G. S. Hammond*, *J. Saltiel*, *A. A. Lamola*, *N. J. Turro*, *J. S. Bradshaw*, *D. O. Cowan*, *R. C. Counsell*, *V. Vogt*, and *C. Dalton*, J. Amer. Chem. Soc. 86, 3197 (1964); b) *G. S. Hammond*, *P. Wyatt*, *C. D. DeBoer*, and *N. J. Turro*, *ibid. 86*, 2532 (1964); *G. S. Hammond* and *R. S. Cole*, *ibid. 87*, 3256 (1965).

[85] *E. F. Ullman* and *N. Baumann*, J. Amer. Chem. Soc. *90*, 4158 (1968); *92*, 5892 (1970).

[86] a) *G. A. Crosby*, *R. E. Whan*, and *R. M. Alire*, J. Chem. Phys. *34*, 743 (1961); b) *M. L. Bhaumik* and *M. A. El-Sayed*, *ibid. 42*, 787 (1965).

[87] a) *O. Schnepp* and *M. Levy*, J. Amer. Chem. Soc. *84*, 172 (1962); b) *A. A. Lamola*, *P. A. Leermakers*, *G. W. Byers*, and *G. S. Hammond*, *ibid. 87*, 2322 (1965); c) *N. Filipescu* and *J. M. Menter*, J. Chem. Soc. *B1969*, 616.

[88] a) *S. A. Latt*, *H. T. Cheung*, and *E. R. Blout*, J. Amer. Chem. Soc. *87*, 995 (1965); b) *L. Stryer* and *R. P. Haugland*, Proc. Nat. Acad. Sci. USA *58*, 719 (1967); c) *R. A. Keller* and *L. J. Dolby*, J. Amer. Chem. Soc. *89*, 2768 (1967); d) *R. A. Keller*, *ibid. 90*, 1940 (1968); e) *J. R. DeMember* and *N. Filipescu*, *ibid. 90*, 6425 (1968).

[89] *D. O. Cowan* and *A. A. Baum*, J. Amer. Chem. Soc. *93*, 1153 (1971), and references therein.

[90] a) *D. F. Roswell*, *V. Paul*, and *E. H. White*, J. Amer. Chem. Soc. *92*, 4855 (1970); b) *D. R. Roberts* and *E. H. White*, *ibid. 92*, 4861 (1970); c) energy transfer in the bioluminescent systems of coelenterates has been reported recently (*J. G. Morin* and *J. W. Hastings*, J. Cell Physiol. *77*, 313 (1971)).

[91] *H. E. Zimmerman* and *J. S. Swenton*, J. Amer. Chem. Soc. *89*, 906 (1967).

[92] *W. H. Richardson*, *F. C. Montgomery*, and *M. B. Yelvington*, J. Amer. Chem. Soc. *94*, 9277 (1972).

[93] *H. Güsten* and *E. F. Ullman*, Chem. Commun. *1970*, 28.

[94] a) *E. N. Harvey*: Bioluminescence. Academic Press, New York 1952; b) Various authors have pointed out that excited states may be of widespread occurrence in biological systems (*A. Szent-Györgi*, Science *93*, 609 (1941); *R. H. Steele*, Biochemistry *2*, 529 (1963); *G. Cilento*, Photochem. Photobiol. *4*, 1243 (1965); *Th. Förster* in *M. Florkin* and *E. H. Stolz*: Comprehensive Biochemistry. Vol. 22. Elsevier, Amsterdam 1967, p. 61: in this latter case, excited states of charge-transfer complexes were dealt with). The latter three sets of authors also speculated about possible roles for chemically produced excited states in biological systems.

[95] *I. Satoda*, *N. Yoshida*, and *E. Yoshii*, Yakugaku Zasshi *79*, 267 (1959).

[96] *I. Satoda*, *N. Yoshida*, and *E. Yoshii*, Jap. Pat. 4127 (Nippon Shinyaku, Ltd.), April 22, 1960.

[97] *E. J. Breaux* and *E. H. White*, unpublished data.

[98] *F. A. Haskins*, *L. G. Williams*, and *H. J. Gorz*, Plant. Physiol. *39*, 777 (1964).

[99] *C. H. Eugster*, Fortschr. Chem. Org. Naturst. *27*, 261 (1969).

[100] *C. Liebermann* and *O. Bergami*, Ber. Deut. Chem. Ges. *22*, 782 (1889).

[101] *O. Hesse*, Liebigs Ann. Chem. *271*, 180 (1892).

[102] *M. Rico*, *A. Vidal*, and *I. Ribas*, An. Soc. Espan. Fis. Quim. *64B*, 613 (1968), and references therein.

[103] *D. G. O'Donovan* and *P. B. Creedon*, J. Chem. Soc. *C1971*, 1604.

[104] *A. P. Arendaruk*, *N. F. Proskurnina*, and *R. A. Konovalova*, J. Gen. Chem. USSR *30*, 693 (1960).

[105] *M. Qudrat-i-Khuda*, *M. E. Ali*, and *L. A. M. Samsuzzaman*, Sci. Res. (Dacca) *2*, 8 (1965).

[106] *F. Santavy*, Biol. Listy *31*, 246 (1951).

[107] *A. A. Lamola*, Biochem. Biophys. Res. Commun. *43*, 893 (1971).

[108] *R. B. Setlow*, Progr. Nucl. Acid Res. Mol. Biol. *8*, 257 (1968).

[109] *E. J. Breaux* and *E. H. White*, unpublished data. Various strains of histidine requiring mutants were used. We thank Prof. *Philip E. Hartman* (Department of Biology, The Johns Hopkins University) for these measurements.

[110] *J. S. Cook*, Photochem. Photobiol. *6*, 97 (1967).

[111] *J. S. Cook* in *A. C. Giese*: Photophysiology. Vol. V. Academic Press, New York 1970, p. 191.

[112] *D. M. Jerina*, *D. R. Boyd*, and *J. W. Daly*, Tetrahedron Lett. *1970*, 457.

[113] *K. Kumaki*, *S. Hata*, *K. Mizuno*, and *S. Tomioka*, Chem. Pharm. Bull. *17*, 1751 (1969).

[114] *R. Breslow*, Chem. Soc. Rev. *1*, 553 (1972).

[115] *E. C. Smith* and *D. E. Metzler*, J. Amer. Chem. Soc. *85*, 3285 (1963).

[116] *C. E. Bills*, J. Biol. Chem. *72*, 751 (1927).

[117] *K. B. Cumming*, Ph. D. Dissertation, Department of Biology, Harvard University 1965.

[118] *G. A. Blondin*, *B. D. Kulkarni*, and *W. R. Nes*, J. Amer. Chem. Soc. *86*, 2528 (1964).

[119] *S. B. Hendricks* in *A. C. Giese*: Photophysiology. Vol. I. Academic Press, New York 1964, p. 305.

[120] *R. K. Clayton*: Light and Living Matter. Vol. 2. McGraw-Hill, New York 1972, p. 113.

[121] *D. H. Hug* and *D. Roth*, Photochem. Photobiol. *16*, 203 (1972).

[122] *J. A. Pettus, Jr.* and *R. E. Moore*, Chem. Commun. *1970*, 1093.

[123] *N. P. Buu-Hoï* and *S. S. Sung*, Naturwissenschaften 57, 135 (1970).

[124] *P. O. P. Ts'o* and *P. Lu*, Proc. Nat. Acad. Sci. USA *51*, 272 (1964).

[125] *L. Santamaria*, *G. G. Giordano*, *M. Alfisi*, and *F. Cascione*, Nature *210*, 824 (1966).

[126] a) *E. A. Mayeda* and *A. J. Bard*, J. Amer. Chem. Soc. *95*, 6223 (1973); b) *C. S. Foote*, *S. Wexler*, *W. Ando*, and *R. Higgins*, *ibid. 90*, 975 (1968).

[127] *K. Gollnick*, Advan. Photochem. *6*, 1 (1968).

[128] *P. Wieland* and *V. Prelog*, Helv. Chim. Acta *30*, 1028 (1947).

[129] *D. Dvornik*, *M. Kraml*, *J. Dubuc*, *M. Givner*, and *R. Gaudry*, J. Amer. Chem. Soc. *85*, 3309 (1963).

[130] *T. Matsuura*, *H. Matsushima*, and *R. Nakashima*, Tetrahedron 26, 435 (1970).

[131] *J. E. Baldwin*, *H. H. Basson*, and *H. Krauss, Jr.*, Chem. Commun. *1968*, 984.

[132] *T. Wilson*, Photochem. Photobiol. *10*, 441 (1969).

[133] *D. M. Jerina*, *J. W. Daly*, *A. M. Jeffrey*, and *D. T. Gibson*, Arch. Biochem. Biophys. *142*, 394 (1971).

[134] *D. T. Gibson*, *G. E. Cardini*, *F. C. Maseles*, and *R. E. Kallio*, Biochemistry *9*, 1631 (1970).

[135] *A. M. Reiner*, J. Bacteriol. *108*, 89 (1971).

[136] *R. C. Allen*, *R. L. Stjernholm*, and *R. H. Steele*, Biochem. Biophys. Res. Commun. *47*, 679 (1972); see also *K. Goda*, *J. Chu*, *T. Kimura*, and *A. P. Schaap*, *ibid. 52*, 1300 (1973); *J. Stauff* and *J. Ostrowski*, Z. Naturforsch. *22b*, 734 (1967).

[137] *H. W. S. Chan*, J. Amer. Chem. Soc. *93*, 4632 (1971).

[138] *H. W. S. Chan*, J. Amer. Chem. Soc. *93*, 2357 (1971).

[139] a) *I. R. Politzer*, *G. W. Griffin*, and *J. L. Laseter*, Chem. Biol. Interactions *3*, 73 (1971); b) *T. Wilson* and *J. W. Hastings* in *A. C. Giese*: Photophysiology. Vol. V. Academic Press, New York 1970, p. 50.

[140] *R. B. Brundrett* and *E. H. White*, unpublished data.

[141] *C. C. Wei* and *E. H. White*, unpublished data.

The Crystalline State of Macromolecular Substances

By H. G. Zachmann[*]

Unlike low molecular weight substances, high polymers do not crystallize completely. However long the crystallization process is continued, they still consist of a mixture of crystalline and noncrystalline regions. In the undrawn material, these regions form larger units which are known as spherulites. Questions that are of special interest concern the arrangement of the chains in the noncrystalline regions, the causes of chain folding, and the imperfections in the crystals. The incomplete crystallization is a consequence of kinetic inhibitions. This can be deduced from the fact that the crystalline fraction increases with rising crystallization temperature. If polymerization is carried out in the solid crystalline state, one obtains a completely crystalline polymeric material.

1. Introduction

Macromolecular substances are becoming increasingly important to science and technology as plastics, as fibers, and as bearers of the processes of life. Consequently they have been and still are the subjects of many investigations. We shall be concerned here with only one aspect of their properties, *i.e.* their crystallization behavior.

The study of the crystallization of macromolecular substances is of the utmost scientific interest, since it shows how the order in the crystal is affected if the molecules, instead of being small spheres as they are in low molecular weight substances, are long chains. However, crystallization processes are also of considerable importance to technology, since the mechanical properties of macromolecular plastics and fibers are strongly dependent on the crystallization conditions. Finally, crystal-like ordered states of macromolecules and their transitions are also important in biological processes.

2. The Crystalline State in Unoriented Material

2.1. General Survey

We shall first consider the crystalline state obtained under normal conditions, *e.g.* when a molten macromolecular substance is cooled to a temperature below its melting point. X-ray investigation of the crystalline structure formed in these circumstances yields a diffraction pattern (Fig. 1) with isolated, relatively broad reflections and a diffuse scattering that is often referred to as an "amorphous halo".

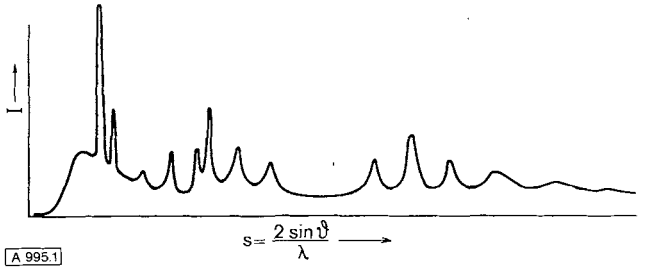


Fig. 1. X-ray large-angle scattering from crystalline polyethylene [1]. The scattering intensity I is plotted as a function of the quantity $s = \frac{2 \sin \vartheta}{\lambda}$, which is a measure of the scattering angle ϑ.

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How is this diagram to be interpreted? An ideally crystalline low molecular weight substance gives a large number of very sharp reflections and no diffuse background. The fact that crystal reflections are obtained for our material shows that some crystallization has occurred. At the same time, however, the small number of reflections and their relatively large half-width indicate that the crystallites are small and highly distorted. Finally, from the presence of the diffuse background, which agrees with the diffraction of the melt, it follows that noncrystalline regions are present as well as the crystallites. *When crystallized as far as possible, therefore, the macromolecular substance is a two-phase system of crystalline and noncrystalline regions.* This result is also confirmed by investigations with other methods, *e.g.* IR spectroscopy, density determination, calorimetry, and nuclear magnetic resonance[2].

An important parameter for the characterization of the two-phase system is the weight fraction of crystalline regions, known as the *crystalline fraction* or the *degree of crystallinity* α. The degree of crystallinity that can be reached is dependent on the crystallization temperature. The degrees of crystallization that can be attained at low temperatures are much lower than those obtained at higher temperatures. This suggests that crystallization remains incomplete for kinetic reasons. After part of the material has crystallized, the mobility of the parts of the chains that have not yet been incorporated into crystallites is so low that they can no longer become ordered. This is in agreement with the fact that an isothermal crystallization has no precisely defined end; the crystallization rate simply becomes steadily smaller, until finally no further crystallization takes place within a finite time.

Table 1. Maximum attainable degree of crystallization α_{max} of some polymers.

Substance	α_{max}
High-density polyethylene	95 %
Low-density polyethylene	70 %
Polyethylene terephthalate	70 %
Nylon 6	60 %
Atactic polystyrene	0 %

The degree of crystallization reached depends not only on the crystallization conditions but also on the chemical structure of the macromolecular substance. Molecules with a high degree of regularity coupled with very high chain mobility can crystallize to a much greater extent than molecules that

do not satisfy these conditions. To illustrate this, Table 1 shows the maximum degrees of crystallization attainable in a number of macromolecular substances. For example, polyethylene, which has very regular, highly mobile molecules, can reach a significantly higher degree of crystallization than polyethylene terephthalate, whose molecules contain rather immobile benzene molecules. Atactic polystyrene, whose molecules have an extremely irregular structure, cannot crystallize at all.

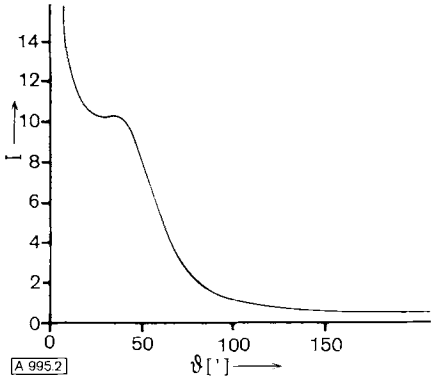


Fig. 2. X-ray small-angle scattering (arbitrary units) from crystalline polyethylene terephthalate. The scattering intensity I is plotted as a function of the scattering angle ϑ [3].

Further details regarding the semicrystalline structure are obtained from the X-ray small-angle scattering. An example of a scattering curve is shown in Figure 2. It shows diffuse scattering that decreases as the scattering angle increases, with a reflection (or in some cases two reflections) superimposed on it. The presence of the reflection is explained by periodic density variations in the material, which are attributed to an alternation of the crystallites and the noncrystalline regions (see Fig. 3). The distance between the centers of gravity of the crystallites, *i.e.* the *long period* L, can be found from the position of the reflection. These investigations lead on the whole to the following conclusions: The centers of gravity of the crystallites are separated by a fairly uniform distance L in the semicrystalline structure. The higher the crystallization temperature, the greater is this distance; it is generally between 50 and 500 Å.

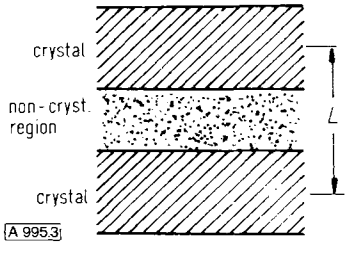


Fig. 3. Schematic representation of the arrangement of the crystallites and the noncrystalline regions. L = long period.

It is especially interesting to compare the above with the results of a microscopic investigation of the crystalline material. If a film about 100 µm thick is examined in polarized light between crossed Nicols, the specimen is found to be completely packed with spherulites. In the simplest case, these are radially symmetrical structures with a black cross. An example is shown in Figure 4. During the crystallization, these spherulites have grown from individual nuclei. They were initially spherical, and the irregular shapes developed only through mutual interference. The diameter of a spherulite is generally 5 to 100 µm. Since the distance between the centers of gravity of the crystallites is of the order of 100 Å, a spherulite consists of a large number of crystalline and noncrystalline regions. To explain the black cross mentioned above, it must be assumed that the crystallites are arranged in such a way that the chains are preferentially normal to the radius of the spherulite.

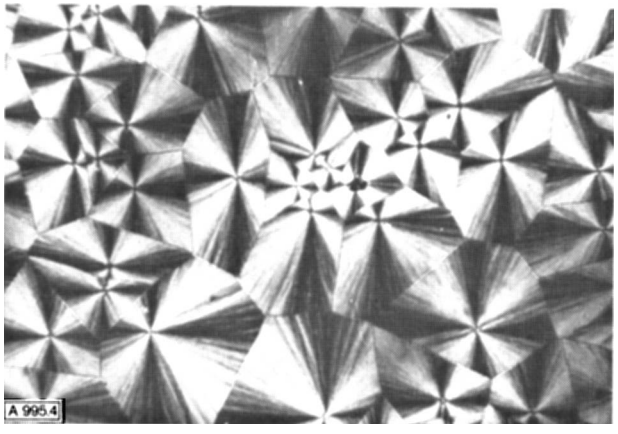


Fig. 4. Polarization micrograph of spherulites in a polyamide [4].

Further information about the fine structure of the spherulites is obtained by electron microscope studies. It is possible to distinguish two types of spherulite:

1. Spherulites built up from fibrils, *i. e.* long filament-like structures. A bundle of fibrils is clearly visible in Figure 5.

2. Spherulites built up from lamellas. The steps between the individual lamellas are clearly visible in Figure 6.

The height of the steps generally agrees with the distance between the centers of gravity of the crystallites as found from the X-ray small-angle scattering. The fibrils in Figure 5 are degenerate lamellas, *i. e.* lamellas that have grown much more strongly in one direction than in the other.

In addition to the simple spherulites shown in Figure 4, there are also spherulites that exhibit complicated birefringence phenomena, as illustrated in Figure 7. If the density of crystal nuclei is high, the spherulites may be so small that they cannot be resolved under the optical microscope. Instead

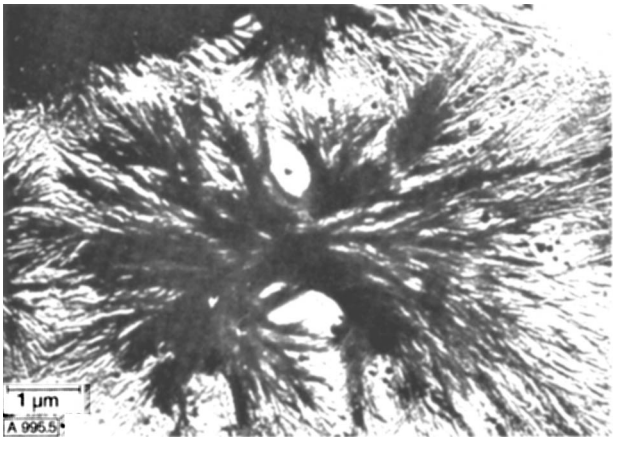


Fig. 5. Electron micrograph of a spherulite in a polyamide [5].

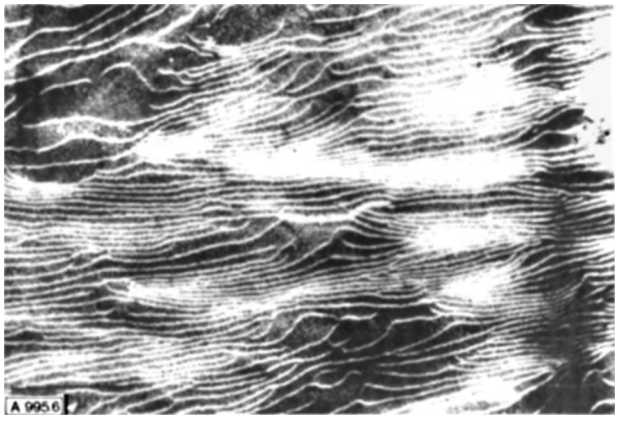


Fig. 6. Electron micrograph of part of a spherulite in high-density polyethylene [6].

of true radially symmetrical spherulites, other units, which may be regarded as precursors of spherulites, are often formed in this case.

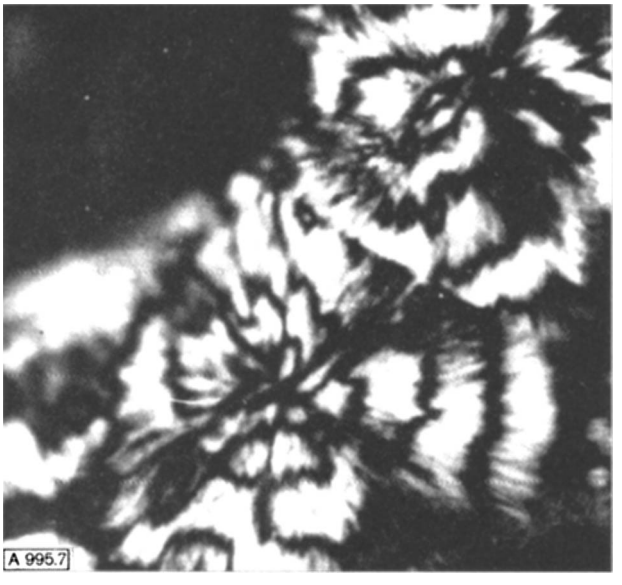


Fig. 7. Polarization micrograph of a spherulite in polyethylene terephthalate [7].

What model can now be given for the structure of a crystalline macromolecular substance? The construction from spherulites, which themselves consist of crystalline and noncrystalline regions, is shown schematically once again in Figure 8. The large polygons bounded by the longer straight lines are the spherulites, the shaded blocks are the crystallites, and the dotted areas are the noncrystalline regions. Figure 8 is not intended to provide any information about the size and position of the crystallites or the nature of the noncrystalline regions. The models that have been proposed are shown in Figure 9 for a small section of a spherulite in each case.

The earliest model is shown in Figure 9a. It shows crystallites that consist of chain segments stretched out parallel to one another, and noncrystalline regions that consist of chain segments passing from one crystallite to another. A lamella or fibril as observed in the electron microscope consists of a crystallite with the associated non-crystalline covering layer. In the second model (Fig. 9b), it is assumed that the chains are folded on the top surfaces and base surfaces of the crystallites; the noncrystalline regions are formed here by a few chain segments that do not fold. According to the last model (Fig. 9c), loops protruding from the surfaces of the crystallites form the noncrystalline regions. (For the sake of clarity, only two loops of this type are shown.) Folding of the chains as indicated in Figures 9b and 9c does not seem very likely at first sight. There is conclusive proof, however, that folding

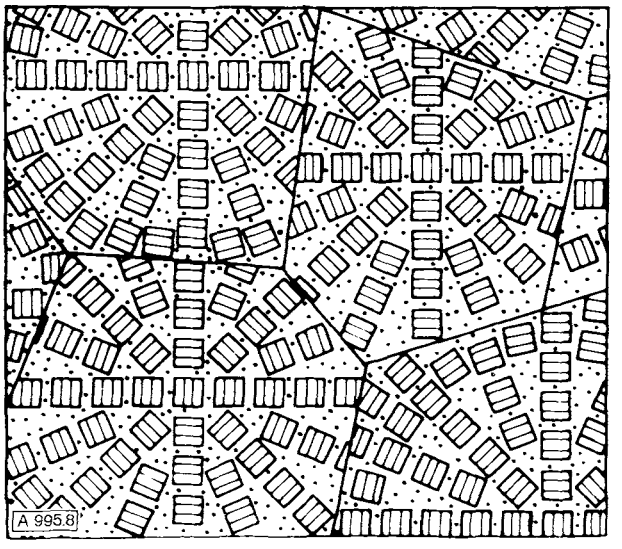


Fig. 8. Schematic representation of the manner in which a spherulite is built up from crystalline and noncrystalline regions [8].

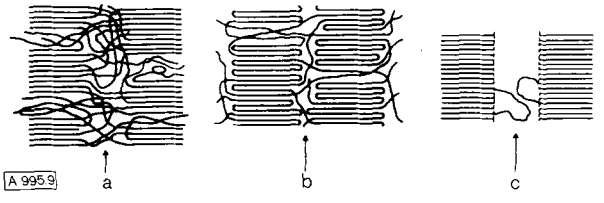


Fig. 9. Models for the noncrystalline regions [9]; for details see text. The arrow shows the direction of the radius of the spherulite.

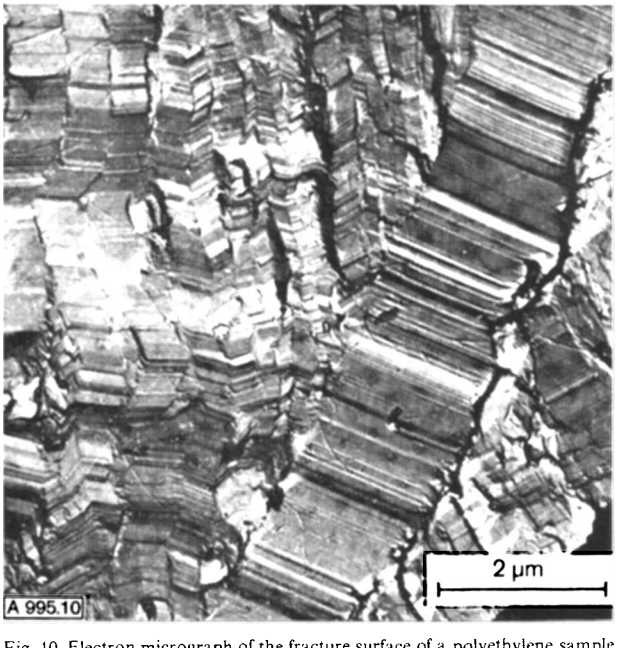


Fig. 10. Electron micrograph of the fracture surface of a polyethylene sample that has been crystallized under a pressure of a few thousand atm [12].

of this type occurs during crystallization from solution[9-11], and there are many indications that it is also possible during crystallization from the melt[6].

The results reported so far were concerned with crystallization under normal pressure. Particularly interesting effects are obtained upon crystallization under a pressure of several thousand atmospheres[12]. Crystallization then proceeds almost to completion; the crystals consist of extended chains. Figure 10 shows an electron micrograph of such a material. The step height corresponds to the thickness of the crystallites, which in turn is equal to the length of the molecules.

Now that we have given a general picture of the experimental results obtained so far and the models proposed, what are the problems that are attracting most attention at present? It seems to me that interest is centered on the following questions:

What kinds of crystal defects are present in the crystallites?

What is the structure of the noncrystalline regions?

How can one explain the folding of the chains and the formation of the spherulites?

We shall now consider these questions in more detail.

2.2. Current Problems

2.2.1. Crystal Defects

The crystalline reflections are broader and less numerous for macromolecular substances than for low molecular weight substances. This must be attributed to the small size of the crystallites and to a particularly high content of defects. In the study of the influence of lattice distortions on the crystalline reflections, according to *Hosemann*[13], the following distortions must be distinguished:

1. Lattice distortions of the first order. These are distortions in which the long-range order is preserved, *e.g.* displacements due to thermal motion.

2. Lattice distortions of the second order, which are also known as paracrystalline distortions. The long-range order is disturbed by these distortions. If they become very pronounced, the crystal changes into a liquid.

Low molecular weight substances exhibit mainly lattice distortions of the first order, whereas high polymers also contain distortions of the second order. By analysis of the half-widths and intensities of the crystalline reflections, it is possible in principle[14] to determine the contributions of the distortions separately.

How are the distortions to be explained at a molecular level? In low molecular weight substances, for example, one finds lattice vacancies, atoms in interstitial sites, dislocations, *etc.* In macromolecular substances there are distortions that are characteristic of chain molecules, and that are known as kinks. These have been intensively studied by *Pechhold*, *Blasenbrey*, and *Woerner*[15]. In an extended chain of CH_2 groups, a kink is formed if a CH_2 group is rotated about an adjacent C—C bond. The sequence of *trans* conformations is then interrupted by a *gauche* conformation. Figure 11 shows schematically an extended chain of C atoms, a chain with a kink, and a chain with a double kink. Figure 12 shows Stuart models of such kinks in polyethylene crystals. Other lattice distortions that are characteristic of substances consisting of chain molecules result from the incorporation of end groups or branching points into the lattice. The defects change the lattice not only at the points where they occur, but also over fairly wide areas in the vicinity of these points. In particular, they cause the above-mentioned paracrystalline distortions. Efforts are being made at present to find a quantitative explanation for the X-ray findings in which the defects are taken into account.

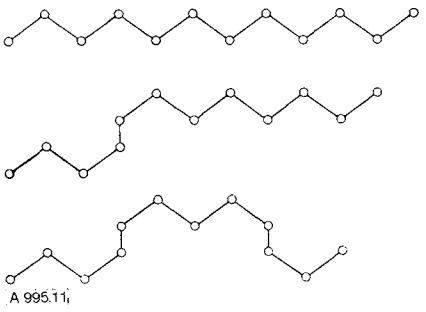


Fig. 11. Chain of carbon atoms a) in the extended state, b) with a kink, and c) with a double kink [15].

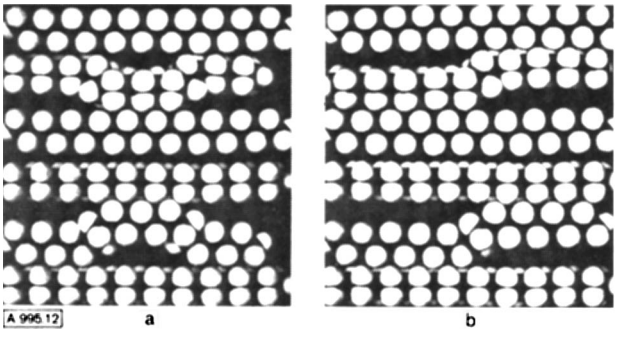


Fig. 12. Stuart models of a) double kinks and b) kinks in a polyethylene crystal [15].

Finally, it should be pointed out that kinks and lattice vacancies are not only formed as a result of disturbances during crystallization, but also arise in thermodynamic equilibrium as a result of thermal motion in an initially ideal crystal. The higher the temperature, the greater is their concentration. *Pechhold* and *Blasenbrey*[16] have established by statistical-thermodynamic calculations that in polyethylene at thermodynamic equilibrium close to the melting point, kinks account for about 1% of the CH_2 groups. The content can of course be considerably higher if the system is not in equilibrium. The number of lattice vacancies at thermodynamic equilibrium has been estimated by *Eby*[17].

2.2.2. Structure of the Noncrystalline Regions

One can only speculate concerning the structure of the noncrystalline regions. The main questions under discussion are as follows: What is the fraction of the tie molecules, that are molecules which connect two crystallites and what is the fraction of loops (see Fig. 9b and 9c)? How long are the loops and what is the distance between their ends? Are there ideal folds present? Efforts have been made to answer these questions directly by IR spectroscopic studies[18,19] and by specific chemical attack on the top surface of the crystallites[20,21]. However, the results were sometimes contradictory.

Some indirect investigations on this problem will now be described.

One of the most effective methods for the study of the nature of the noncrystalline regions is the measurement of the absolute intensity of the X-ray small-angle scattering. The scattering intensity I is measured as a function of the scattering angle ϑ or the derived quantity

$$s = \frac{4\pi}{\lambda} \sin \frac{\vartheta}{2}$$

The following equation is then valid[22]:

$$\int I(s) s^2 \, ds = C \times (\rho_k - \rho_a)^2 \alpha (1 - \alpha) \qquad (1)$$

where ρ_k is the density of the crystallites, and ρ_a is the density of the non-crystalline regions, α is the crystalline fraction, and C is a constant that depends on the experimental arrangement and the intensity of the primary beam. Thus experimental determination of the integral on the left-hand side of the equation yields additional information about the densities of the crystallites and of the noncrystalline regions.

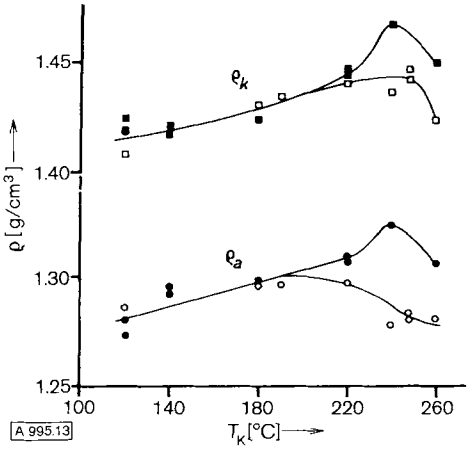


Fig. 13. Densities of the crystallites ρ_k and of the noncrystalline regions ρ_a in polyethylene terephthalate as a function of the crystallization temperature T_K. ■ and ● : Samples cooled slowly after crystallization. □ and ○ : Samples quenched after crystallization [3].

Fischer, *Goddar*, and *Schmidt*[23] were the first to apply this method to problems of the crystalline state. These authors were able to show that the usual assumptions for ρ_a and ρ_k are valid for undrawn polyethylene, but not for the drawn material. Our investigations on polyethylene terephthalate showed that ρ_a and ρ_k do not have the normally assumed values for this material even in the undrawn state. The values found for ρ_k and ρ_a under certain additional assumptions are shown in Figure 13 as functions of the crystallization temperature. Both quantities are strongly dependent on the crystallization temperature. The density of the noncrystalline regions is generally lower than that of the completely amorphous material, which is 1.331 g/cm³. This indicates in particular that the structure of the noncrystalline regions is strongly dependent on the crystallization temperature.

A particularly interesting result was obtained by *Fischer*, *Kloos*, and *Lieser*[24] for polyethylene single crystals. A question that has often been considered is whether the loops protruding from such crystals have the same properties as compact amorphous material. These authors determined the difference between the densities of crystalline and of noncrystalline regions in the single crystals as a function of temperature. The intensity of the X-ray small-angle scattering, which, according to eq. (1), is a measure of this density difference $\rho_k - \rho_a$, is shown as a function of temperature in Figure 14. $\rho_k - \rho_a$ is almost constant up to a certain temperature, beyond which it increases with rising temperature. The temperature at which the curve changes direction agrees well with the glass transition temperature of the amorphous substance. This result may be regarded as evidence that loops projecting from the crystallites behave as completely amorphous material with regard to the glass transition phenomena.

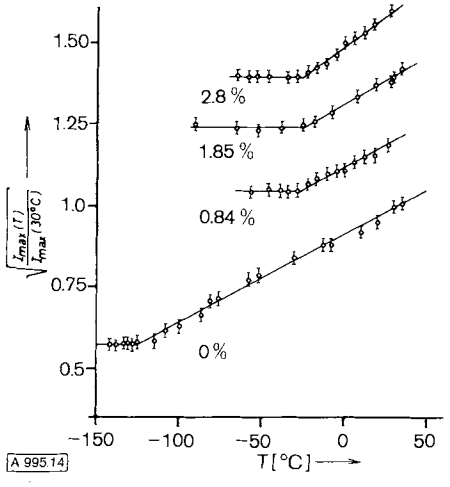


Fig. 14. Temperature dependence of the intensity of the X-ray small-angle scattering from polyethylene single crystals [24] with various contents of methyl groups (values in mole %). $\sqrt{I_{max}(T)/I_{max}(30\,°C)}$ is a measure of the density difference $\rho_k - \rho_a$.

Valuable information about the nature of the noncrystalline regions can be obtained with the aid of nuclear magnetic resonance. Parts of the chain that can undergo segmental motion lead to a narrow component in the NMR signal, while parts that cannot change their conformations lead to a broad component. In a semicrystalline substance above the glass transition temperature, the ^{1}H-NMR signal consists of two components:

1. a narrow component due to chains possessing sufficiently high segment mobility in the noncrystalline regions,

2. a broad component due to the chains in the crystals and to strongly restrained and hence immobile chains in the noncrystalline regions.

The fraction of the area under the narrow component therefore represents the "mobile fraction" y. If all the chains in the noncrystalline regions also possess segment mobility, y is equal to the noncrystalline fraction $1-\alpha$. If there are strongly restrained chains in the noncrystalline regions, on the other hand, y is smaller than $1-\alpha$.

Attempts have been made to compare y and $1-\alpha$. The difficulty in every case lay in the accurate separation of the narrow component from the broad component in the NMR signal. We have now developed a method for polyethylene terephthalate[25] that avoids an arbitrary separation. We have used this method to determine the mobile fraction y from the nuclear magnetic resonance. $1-\alpha$ was then determined from

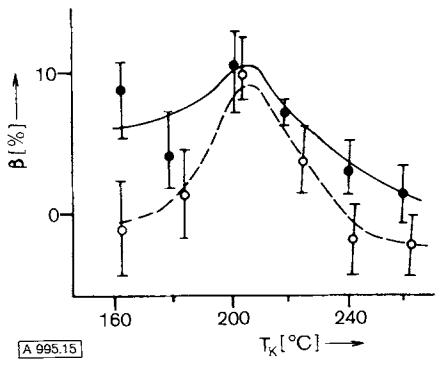


Fig. 15. Rigid noncrystalline fraction $\beta = 1 - \alpha - y_x$ as a function of the crystallization temperature of polyethylene terephthalate [25]. •: Quenched, o: cooled slowly.

the density of the noncrystalline fraction. The difference between the two quantities, which corresponds to the rigid noncrystalline fraction β, is shown in Figure 15 as a function of the crystallization temperature T_k. In the slowly cooled samples, this fraction is practically zero both for low and for high crystalline temperatures. For medium crystallization temperatures, where the crystallization rate is highest, about 5 to 10% of the chains contribute to the rigid noncrystalline fraction. These must be assumed to be chains that join two crystallites and that are relatively highly strained. According to theoretical considerations, the distance between the ends of these chains must be greater than half of the chain length[26]. The rigid noncrystalline fraction β is greater for the quenched samples than for the slowly cooled samples.

Finally, we should mention that the NMR signal has also been separated by various authors into more than two components and interpreted accordingly[27].

2.2.3. Theoretical Interpretation of Chain Folding

A question that is particularly difficult is why the chains fold during crystallization. If the material crystallizes from a dilute solution, in which the crystal nucleus practically consists of a single molecule, folding of this molecule is essential[28]. In crystallization from the melt, however, one would expect a crystal nucleus to be formed from several adjacent molecules. This would lead to the formation of bundle nuclei instead of to chain folding. What factors prevent the formation of bundle nuclei (see Fig. 18b)?

We believe that this is due to entropy effects that are characteristic of substances consisting of chain molecules[29]. When a low molecular weight substance crystallizes, an entire molecule passes from one phase into the other (Fig. 16a). The changes in energy and in entropy accompanying the transition are the same for every molecule. On crystallization of a high polymer, on the other hand, only small segments corresponding in size to the monomer unit pass in succession from one phase into the other (Fig. 16b). The entropy change for such a transition can generally differ from one monomer unit to another, since the entropy of the remaining part of the chain that is not incorporated into the crystal also changes.

Some examples are shown in Figure 17. The transition of a monomer unit from the crystal into the melt is considered in each case. The unit in question is indicated by a circle with an arrow. In Figure 17a, the monomer unit belongs, even after melting, to a chain segment with two fixed ends. The entropy gain on melting in this case is smaller than the average value. In Figure 17b, on the other hand, as a result of the transition, a chain segment N with two fixed ends becomes a chain segment with only one fixed end, to which the unit that has melted belongs. The entropy gain on melting is thus greater than average. Yet other situations are found in the melting processes of Figures 17c and 17d.

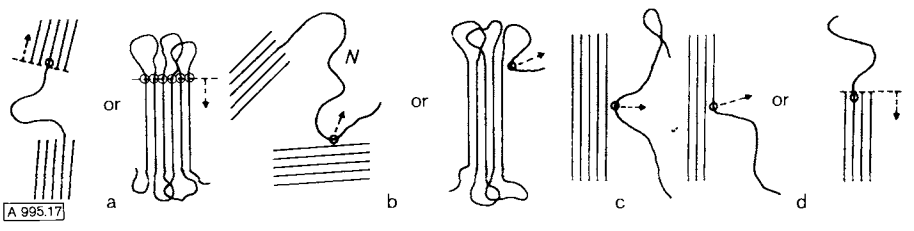


Fig. 17. Examples of the transfer of a monomer unit from the crystal to the melt. For details see text.

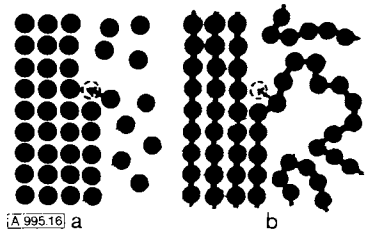


Fig. 16. Schematic representation of the elementary step in the crystallization a) of a low molecular weight substance and b) of a macromolecular substance.

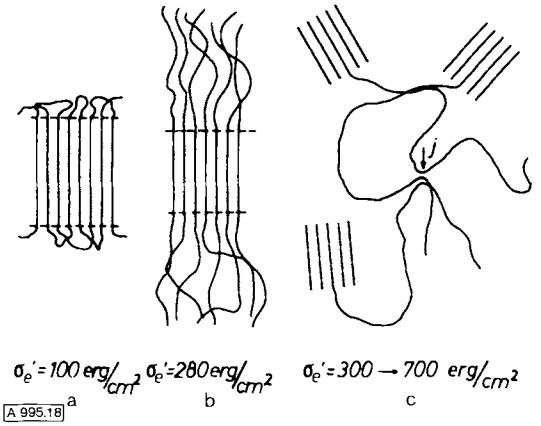


Fig. 18. Additional surface tension σ_e' for various types of nuclei [29]. a) Folded-chain nucleus, b) bundle nucleus, c) nucleus consisting of chains projecting from different crystallites (j = point at which the new nucleus is formed).

These entropy effects have a pronounced influence on the crystal nucleation[29]. For example, if a bundle nucleus is formed (see Fig. 18b) and a new molecule is deposited on

the nucleus, in addition to the changes in the entropy of the monomer units that are just crystallizing, there are also changes in the entropies of the parts of the molecules protruding from the crystals, since the freedom of movement of these tails is restricted by the fact that they are now situated close to the surface of a crystal, and consequently cannot assume so many conformations as before. We have calculated this effect and shown that this acts as an additional surface tension σ'_e ($\approx 280\,erg/cm^2$) during nucleation. An additional surface tension is also present in the case of a folded-chain nucleus (Fig. 18a) because of the folds; however, this amounts to only about $100\,erg/cm^2$. This value already includes an enthalpy contribution of about $60\,erg/cm^2$, which is due to the increased number of *gauche* conformations in a loop. The additional surface tension is particularly high in the case of a crystal nucleus consisting of chains that project from different crystallites (Fig. 18c, $\sigma'_e = 300$ to $700\ erg/cm^2$). A very close relationship exists between the surface tension and the nucleation rate. With increasing surface tension the free energy of nucleation increases, and the nucleation rate consequently decreases. It follows that nuclei with regular short folds are kinetically favored over bundle nuclei.

If the crystallization rate becomes very high, the type of crystal nucleus is no longer determined by the free energy of nucleation. The chains then come together just as they exist in the melt. In this case there is a tendency toward the formation of longer loops with unequal distances between the ends, and of chains that connect different crystallites. The more the molecules penetrate one another in the melt, the greater this tendency becomes[30].

The entropy effects discussed here also play an important role in the explanation of the broad melting range and the superheating phenomena of polymers[28, 31].

3. Drawn Material

So far we have been discussing crystallization under normal conditions. In the manufacture of fibers, it is usual to subject the material to a tensile stress, as a result of which it is drawn to several times its original length. In the course of this drawing process, the molecules become preferentially oriented parallel to the drawing direction. The drawing may be carried out before, simultaneously with, or after crystallization. It is only through this drawing that the fibers acquire the desired technological properties[32].

The changes in structure that occur during the drawing process have been investigated particularly thoroughly by *Balta-Calleja* and *Peterlin*[33]. In the following discussion we shall be concerned only with the structure after the drawing has been completed.

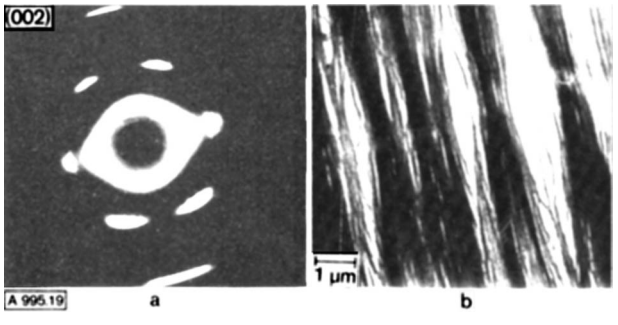


Fig. 19. a) Electron diffraction pattern and b) electron micrograph of a drawn polyethylene film in transmission [34].

The crystalline structure in the drawn material differs considerably from that in the undrawn material. There are no spherulites, but only fibrils. Figure 19b shows an electron micrograph of polyethylene that was drawn after crystallization. One can see individual fibrils, all lying parallel to the drawing direction. The molecules run parallel to the fibrils, as is shown by electron diffraction patterns (Fig. 19a). These fibrils give the fibers their well-known high mechanical strength[35].

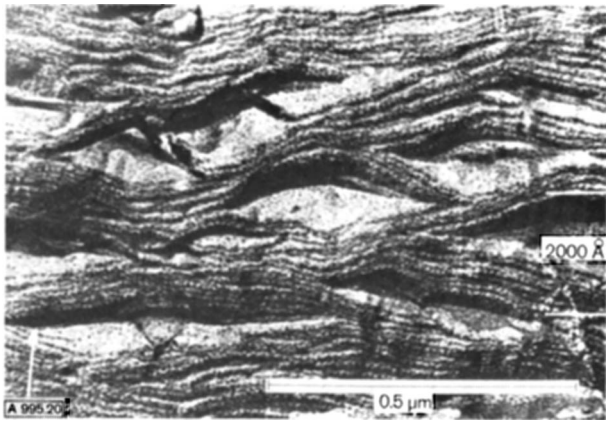


Fig. 20. Electron micrograph of a polyethylene film drawn in the direction of the arrow and annealed for 1 hour at 125 °C after drawing [36].

If the material is annealed after drawing, a distinct structure develops in the lengthwise direction[36]. Figure 20 shows the state at the end of this process. One now finds lamellar structures extending predominantly normal to the drawing direction. A possible interpretation of this process is shown in Figure 21. Immediately after drawing, the noncrystalline

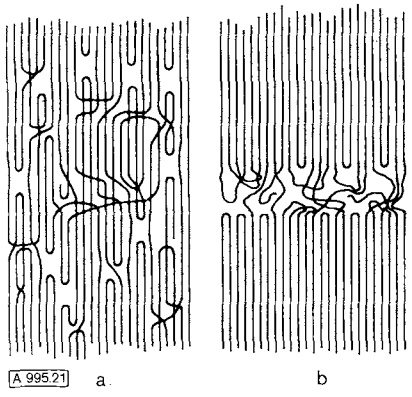


Fig. 21. Schematic representation of the structure of a) unannealed and b) annealed drawn polyethylene [36].

regions are widely distributed, and have the character of small defects (Fig. 21a). During annealing, these defects come together in layers, with the result that a lamellar structure is formed (Fig. 21b).

4. Crystallization During Polymerization in the Solid State

The discussions so far have been concerned with the crystallization of a material from the amorphous state. In this type

of crystallization, the initially coiled and entangled chains must become ordered. One can understand that considerable kinetic inhibitions occur here, and that the crystallization, as described, consequently does not proceed to completion.

Quite recently, the direct transformation of a low molecular weight crystal into one with a high molecular weight by polymerization in the solid state has been achieved. For example, when crystals of the bis(*N*-phenylurethane) of 2,4-hexadiyne-1,6-diol are exposed to ultraviolet light or X-rays, the molecules polymerize and the triple bonds simultaneously turn as indicated in Figure 22. The macromolecules are produced directly

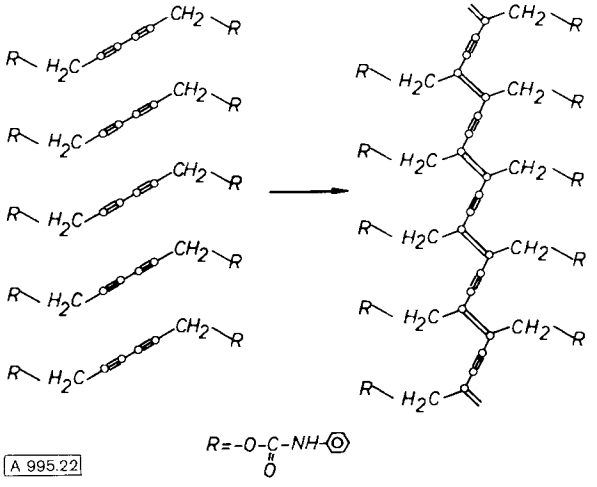


Fig. 22. Change in the position of the CC triple bonds (C≡C) on polymerization of the bis(*N*-phenylurethane) of 2,4-hexadiyne-1,6-diol [2,4-hexadiynylene bis(*N*-phenylcarbamate)].

in the form in which they are present in the crystal[37, 38]. It is not surprising, therefore, that a completely crystalline material is obtained in this case in the form of large single crystals, which do not differ in any way from low molecular weight substances as far as crystalline order is concerned. Figure 23 shows the single crystals obtained, which are many

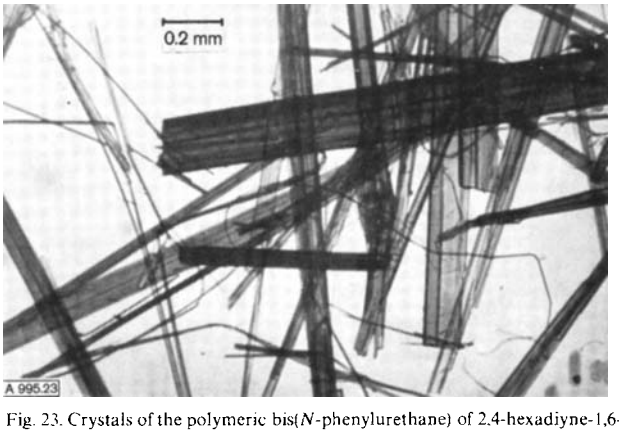


Fig. 23. Crystals of the polymeric bis(*N*-phenylurethane) of 2,4-hexadiyne-1,6-diol obtained by polymerization in the solid state.

times as large as the single crystals prepared from solution. Figure 24 shows the X-ray diffraction pattern, which exhibits a large number of sharp reflections and no amorphous halo. The direct transformation of a low molecular weight crystal into a high-polymer crystal as in the above example is possible

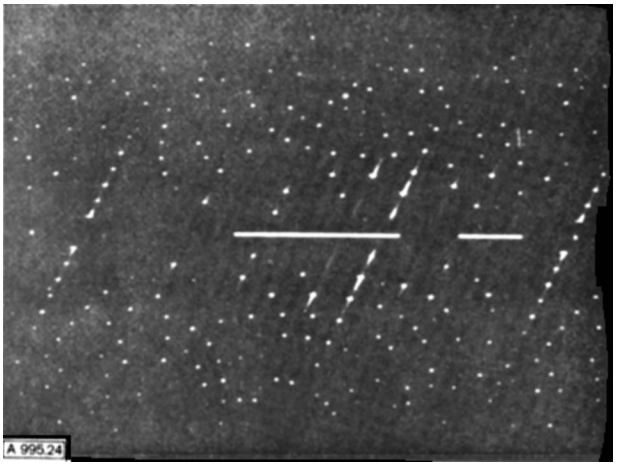


Fig. 24. Weissenberg photograph of the (*hk*0) plane of a polymeric single crystal [38] from Fig. 23.

for only a very small number of substances. It can occur only if the unit cell of the low molecular substance is identical with that of the high molecular weight substance. Substances for which this condition is not satisfied, such as acrylic and vinyl compounds, can apparently also be polymerized in the solid state. However, a liquid phase is presumably formed as an intermediate state during the polymerization[39]. The polymer obtained in such cases, as in a crystallization from the melt, is only partly crystalline.

5. Outlook

The fact that it has been possible to produce ideal crystals of macromolecular substances is very important. It shows that macromolecular substances, in principle, can crystallize completely, and that incompleteness in the crystallization from the melt is due to kinetic inhibition. At the same time, however, it must be emphasized that incomplete crystallization is not merely a fascinating subject for scientific investigation, but is also responsible for some outstanding properties of the macromolecular substances. Incomplete crystallization is the reason for the high strength of fibers coupled with flexibility, the ductility of films, and the low tendency of injection molded material to fracture. An ideal crystal is brittle, is practically inextensible, and shatters easily. It can achieve technical importance only in fields different from those in which the semicrystalline material is important, *e.g.* in the semiconductor field.

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[1] *H. G. Kilian*, Kolloid-Z. Z. Polym. *183*, 1 (1962).
[2] See, *e.g.*, *H. G. Zachmann*, Fortschr. Hochpolym.-Forsch. *3*, 581 (1964).
[3] *G. Konrad* and *H. G. Zachmann*, Kolloid-Z. Z. Polym. *247*, 851 (1971).
[4] *E. W. Fischer*, unpublished.
[5] *H. A. Stuart* and *B. Kahle*, unpublished.
[6] *E. W. Fischer*, Discuss. Faraday Soc. *25*, 205 (1958).
[7] *A. Keller*, J. Polym. Sci. *17*, 291 (1955).
[8] *H. G. Zachmann*, Faserforsch. Textiltech. *18*, 427 (1967).
[9] *A. Keller*, Phil. Mag. *2*, 1171 (1957).
[10] *E. W. Fischer*, Z. Naturforsch. *12a*, 753 (1957).
[11] *P. H. Till*, J. Polym. Sci. *24*, 301 (1957).
[12] *R. B. Prime* and *B. Wunderlich*, J. Polym. Sci. *A-2 7*, 2061 (1969).
[13] *R. Hosemann*, Polymer *3*, 349 (1962).

[14] *R. Hosemann* and *W. Wilke*, Makromol. Chem. *118*, 230 (1968).

[15] *W. Pechhold, S. Blasenbrey*, and *S. Woerner*, Kolloid-Z. Z. Polym. *189*, 14 (1963).

[16] *W. Pechhold* and *S. Blasenbrey*, Kolloid-Z. Z. Polym. *216—217*, 235 (1967).

[17] *R. Eby*, J. Appl. Phys. *33*, 2253 (1962); *34*, 2442 (1963).

[18] *M. I. Bank* and *S. Krimm*, J. Polym. Sci. *B8*, 143 (1970).

[19] *W. O. Statton, J. L. Koening*, and *H. Hannon*, J. Appl. Phys. *41*, 4290 (1970).

[20] *A. Keller* and *S. Sawada*, Makromol. Chem. *74*, 190 (1964).

[21] *G. Meinel* and *A. Peterlin*, J. Polym. Sci. *A-2* 6, 587 (1968).

[22] *G. Porod*, Kolloid-Z. *124*, 83 (1951).

[23] *E. W. Fischer, H. Goddar*, and *G. F. Schmidt*, Makromol. Chem. *118*, 144 (1968).

[24] *E. W. Fischer, F. Kloos*, and *G. Lieser*, J. Polym. Sci. *B7*, 845 (1969); see also *F. Kloos*, Dissertation, Universität Mainz 1972.

[25] *U. Eichhoff* and *H. G. Zachmann*, Ber. Bunsenges. Phys. Chem. *74*, 919 (1970).

[26] *P. Schmedding* and *H. G. Zachmann*, Kolloid-Z. Z. Polym. *250*, 1105 (1972).

[27] *K. Bergmann*, Ber. Bunsenges. Phys. Chem. *74*, 912 (1970).

[28] *J. I. Lauritzen* and *J. D. Hoffmann*, J. Res. Nat. Bur. Stand. *64 A*, 79 (1960).

[29] *H. G. Zachmann*, Kolloid-Z. Z. Polym. *216—217*, 180 (1967); Kolloid-Z. Z. Polym. *231*, 504 (1969).

[30] *W. M. Ewers, H. G. Zachmann*, and *A. Peterlin*, Kolloid-Z. Z. Polym. *250*, 1187 (1972).

[31] *H. G. Zachmann*, Kolloid-Z. Z. Polym. *206*, 25 (1965).

[32] *R. Bonart* and *F. Schulze-Gebhart*, Angew. Makromol. Chem. *22*, 41 (1972).

[33] *A. Peterlin* and *F. J. Balta-Calleja*, Kolloid-Z. Z. Polym. *242*, 1093 (1970).

[34] *E. W. Fischer* and *G. F. Schmidt*, Angew. Chem. *74*, 551 (1962); Angew. Chem. internat. Edit. *1*, 488 (1962).

[35] *A. Peterlin*, IUPAC Symposium Helsinki, July 1972.

[36] *E. W. Fischer* and *H. Goddar*, J. Polymer Sci. *C 16*, 4405 (1969).

[38] *J. Kaiser, G. Wegner*, and *E. W. Fischer*, Isr. J. Chem. *10*, 157 (1972).

[37] *G. Wegner*, Makromol. Chem. *154*, 35 (1972).

[39] *B. Wunderlich*, Adv. Polymer Sci. *5*, 568 (1968).

Mass Spectral Interaction between the Functional Groups of Multiply Substituted Alkanes

By Herbert Bosshardt and Manfred Hesse[*]

The mass spectral decomposition of di- and polyfunctional alkanes is characterized essentially by two, fundamentally different reactions: On the one hand the structures of the fragment ions are determined by separated degradation of each functional group; on the other hand, however, a relatively large number of fragment ions result from the combined action of two or even more functional groups. This special type of fragmentation has become an important topic in today's mass spectral research. In the present progress report an attempt has been made to summarize the results obtained so far.

1. Introduction

Molecules of the aliphatic series of compounds number among the first organic molecules to have been investigated by mass spectroscopy[1]. Although the initial studies on this class of compounds to derive mechanisms for explaining mass spectral decomposition had already begun in the fifties, and though these mechanisms are now generally accepted, renewed interest has been shown in the spectra of aliphatic compounds by organic chemists working on mass spectrometry. Formerly the prime interest was attached to elucidating the influence of one functional group on the decomposition of monofunctional alkanes, today the interest focuses upon the influence which two or more functional groups within a molecule have on the decay of aliphatic compounds. It soon became clear that although a more or less greater portion of the fragment ions, occurring in the spectra of difunctional compounds, can be explained by the fragmentation of each group on its own, *i.e.* independently of each other, the origin of many fragment ions could still not be satisfactorily explained. However, the existence of such ions can be accounted for by assuming the occurrence of direct or indirect interaction between the functional groups.

The interplay of functional groups, separated by several methylene groups, has already been known in preparative chemistry for a long time. Cyclization reactions of many different types can be used as examples to illustrate this.

In order to prevent side reactions taking place during the formation of medium-sized and large-membered rings, very dilute solutions have been used (cf. *e.g.*[2]). Such conditions enhance the possibility that the reaction center under consideration accepts other functional groups of the same molecule as closest neighbor, *i.e.* the conditions are very much akin to those prevalent in mass spectroscopy (high vacuum).

To which type do the mass spectrometric interactions mentioned above belong, and what would their participation indicate? Is it possible to draw important conclusions about the structure of unknown difunctional alkanes on the basis of their special fragmentation? These and similar questions have initiated a number of interesting research papers in recent years. It would not be out of place to mention at the outset that decomposition reactions caused by interaction of two

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or more functional groups would seem to be the rule rather than the exception in the mass spectral decomposition of di- and polyfunctional alkanes.

The fragmentation patterns of compounds with oxygen- and nitrogen-containing functional groups have been studied in detail and constitute the main subject under discussion in the present progress report. These investigations were purposely confined to aliphatic compounds in which the functional groups are connected neither conjugatively nor by rings. This does not infer, however, that alicyclic or aromatic compounds should react differently (such compounds have also been investigated: cf. *e.g. ortho-* and *peri*-effects in aromatic systems[3], in maleic and fumaric acid derivatives[4], in 1,2-dicarboxylic acids from cycloalkanes[5] and cycloalkenes[6], and in cyclohexylsilyl compounds[7]).

2. Interaction between Nitrogen-containing Functional Groups

On comparing the mass spectra of acetylated *n*-alkylamines[8,9] *e.g.* *N*-hexyl-*N*-methylacetamide *(1)* (Fig. 1[8]) with those of *N,N'*-diacetylated α,ω-alkanediamines[8], *eg. N,N'*-tetramethylenediacetamide (*N,N'*-diacetylputrescine) *(2)* (Fig. 2[8]), it is striking that in both cases 43 atomic mass units (amu) are split off from the molecular ion. Thus it would appear—at least at first sight—that there is no principle difference in the fragmentation pattern of mono- and difunctional alkanes. Yet a closer investigation of the two spectra shows

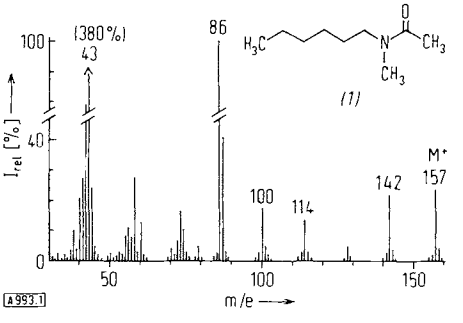


Fig. 1. Mass spectrum of *N*-hexyl-*N*-methylacetamide *(1)* (see Ref. [8]).

that different fragmentation reactions take place[8,9]: In the case of $(1)^{\ddagger}$, loss of $\cdot C_3H_7$ and $\cdot H$ is followed by CH_2CO-fission, while in $(2)^{\ddagger}$ only a loss of $CH_3CO\cdot$ from the molecular ion is observed. Although both compounds contain the same

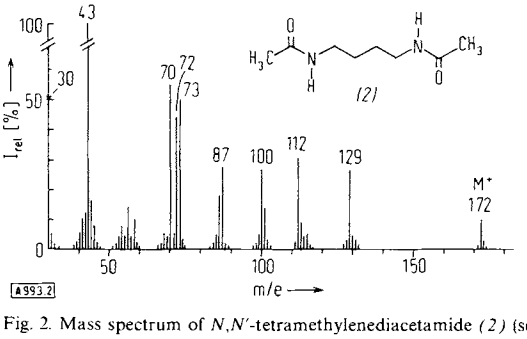
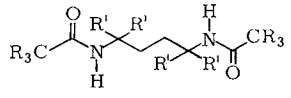


Fig. 2. Mass spectrum of *N,N'*-tetramethylenediacetamide *(2)* (see Ref. [8]).

structural unit ($-CH_2NR-COCH_3$), the ion $[M-43]^+$ is formed *via* basically different routes. It may be concluded that the second amide group of compound *(2)* prevents typical decomposition of the *N*-acetylalkyl residue by interaction, and causes a new mode of decomposition.

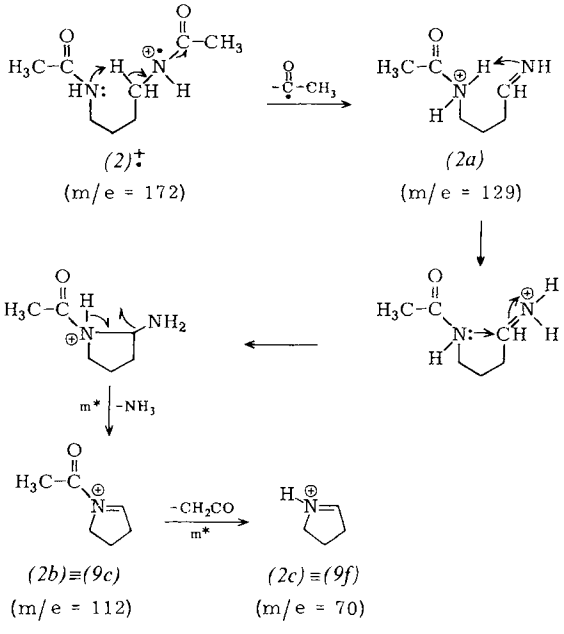
2.1. Loss of *N*-Substituents (R) from the Molecular Ion[8,10,11]

That $\cdot COCH_3$ splits off from the molecular ion in the case of the *N,N'*-diacetyl compound *(2)* has been proved by the determination of the exact mass and by investigation of the deuterated derivatives D_6-*(2)* and D_{10}-*(2)*; the reaction course is illustrated in Scheme 1.



(2), R = R' = H
D_6-*(2)*, R = D, R' = H
D_{10}-*(2)*, R = R' = D

The actual fragmentation is caused by an attack by one end of the chain (N or O) on the α-hydrogen atom to the amide group of the other, the charge-carrying end. If all four α-positions are blocked by methyl groups, *e.g.* in tetramethyl-*N,N'*-tetramethylenediacetamide, loss of $\cdot COCH_3$ from the molecular ion is not observed[12].



Scheme 1

This loss of the acetyl group is not only observed in the putrescine derivative *(2)*, but also in the decomposition of all acetylated diamines in which the nitrogen atoms are separated by a chain of at least three CH_2-members. This chain should allow at least a cyclic transition state—before the actual fragmentation takes place—to make an approach of the two functional groups possible. Thus the $[M-COCH_3]^+$ signal has been detected in all *N,N'*-diacetylated α,ω-alkyldiamines which contain three to sixteen CH_2-groups[*]. The loss of the *N*-substituent is also not confined

[*] Longer chains have not yet been investigated.

to the acetyl residue; many other *N*-substituents behave analogously, *e.g.* alkyl groups (CH_3[8], C_2H_5[8], $C_nH_{2n}R$[13], $CH_2C_6H_5$[8] *etc.*) and other acyl residues (COC_6H_5[8], $COCH_2$—CH_2—C_6H_5[14] *etc.*).

Interesting in this connection are the mass spectra of α,ω-alkyldiamines, whose nitrogen atoms carry more than one substituent. Such compounds can be classified into two groups:

1. Compounds in which both the nitrogen atoms are identical, but are each substituted with two different groups, *e.g.* *N,N'*-diethyl-*N,N'*-tetramethylenediacetamide *(3)* (Fig. 3).

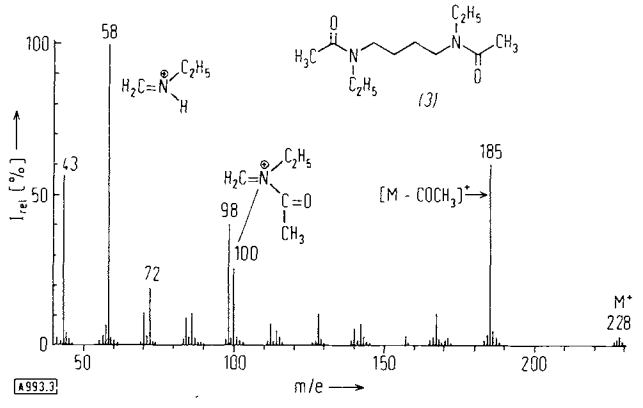


Fig. 3. Mass spectrum of *N,N'*-diethyl-*N,N'*-tetramethylenediacetamide *(3)* (see Ref. [10]).

2. Compounds in which the nitrogen atoms are substituted dissimilarly, *e.g.* *N*-(3-diethylaminopropyl)acetamide *(4)* (Fig. 4).

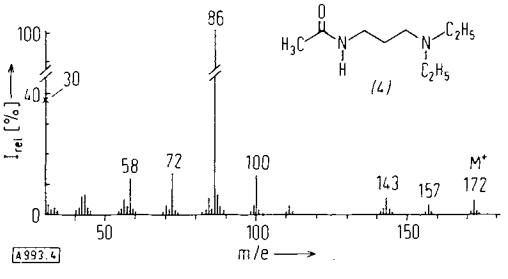


Fig. 4. Mass spectrum of *N*-(3-diethylaminopropyl)acetamide *(4)* (see Ref. [8]).

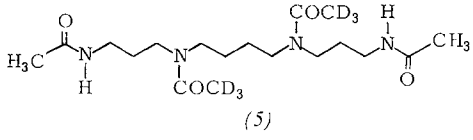
Supposing that the fragmentation reactions involving cleavage of $\cdot C_2H_5$ and $\cdot COCH_3$ are alike, the tendency to lose a *N*-substituent can be estimated from the mass spectra of compounds of the first group[8, 10].

The mass spectrum of *(3)* (Fig. 3[10]) shows only the $[M-COCH_3]^+$ signal and not one at $[M-C_2H_5]^+$. By comparing the abundances of $[M-R]^+$ ions in the mass spectra of other model substances, a sequence was found[8, 13] which illustrates the fission tendency of *N*-substituents (for preparative reasons a direct comparison of acetyl and benzoyl has not yet been possible):

$$H < CH_3 < C_2H_5 < C_nH_{2n}R < CH_2C_6H_5 < COCH_3, COC_6H_5$$

H and CH_3 show the least tendency to split off. Reasons for the different behavior of the radicals are not yet definitely known.

The second case—the two nitrogen atoms of an α,ω-alkanediamine are substituted differently—provides information about charge localization at the moment of cleavage of the substituent R. The spectrum of *(4)* (Fig. 4)[8] indicates only a fission of the ethyl-, but not the acetyl-radical—a result which seems to be contrary to that found in the decomposition of compound *(3)* (Fig. 3). N^1,N^{14}-diacetyl-N^5,N^{10}-bis(trideuterioacetyl)spermine *(5)* eliminates only the central (deuterio)-acetyl group, but not the terminal acetyl groups. Both of the central nitrogen atoms belong to tertiary, the terminal ones to secondary amide groups. If these two findings are correlated with the values given in the literature for the ionization potentials of secondary and tertiary amines and acetamides[*], it can be concluded that substituent is eliminated which is



(5)

attached to the nitrogen atom having the lowest ionization potential, and therefore becomes charge carrier at the moment of fission.—Exceptions concerning this behavior have not been observed in this class of compounds, though a large number of model substances have been investigated.

Within an homologous series of such compounds, the mass spectra are similar, but not alike. Figures 5 and 6 illustrate the dependence of the abundance of $[M-acyl]^+$ ions in *N,N'*-acetylated and *N,N'*-benzoylated homologous α,ω-alkanediamines on the number of chain members.

The curves in the two figures for the cleavage of $\cdot COCH_3$ and $\cdot COC_6H_5$ from the molecular ion run parallel to some extent: the abundance of these ions is lowest in compounds containing five or six CH_2 groups. The abundance increases with the increase in number of CH_2 groups, reaches a maximum value (ten CH_2 groups), and then decreases again. This decrease is presumably determined by the mode of comparison: The relative proportion of $[M-acyl]^+$ ions will decrease with increasing number of chain members.

In the case of the lighter compounds the minimum of the curve for acetamides having five or six CH_2 groups is followed by an increase, which is indicative of a consecutive reaction

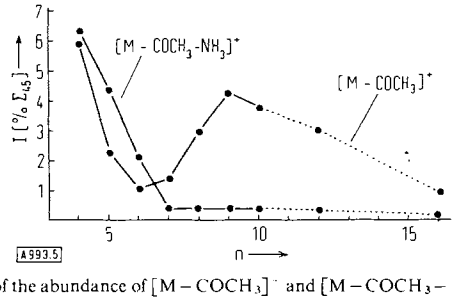


Fig. 5. Dependence of the abundance of $[M-COCH_3]^+$ and $[M-COCH_3-NH_3]^+$ ions on the number *n* of CH_2 groups between the two nitrogen atoms in *N,N'*-diacetylated α,ω-alkanediamines (from 70 eV mass spectra; see Ref. [8]). The abundance refers to the total ion current Σ. It has been calculated only from $m/e = 45$.

[*] Ionization potentials of model compounds: $CH_3CONHCH_3$: 8.90 ± 0.02 eV; $CH_3CON(CH_3)_2$: 8.81 ± 0.03 eV; $(CH_3)_2NH$: 8.24 ± 0.02 eV; $(CH_3)_3N$: 7.82 ± 0.02 eV [15]. (Ionization potentials of the compounds discussed here have not yet been measured.)

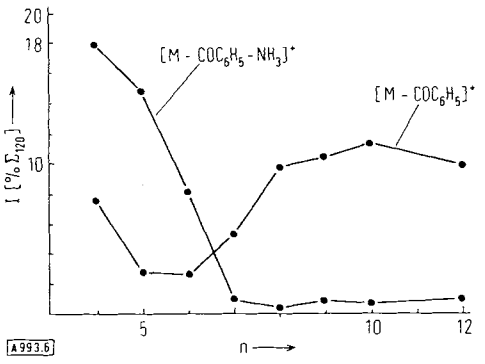


Fig. 6. Dependence of the abundance of $[M-COC_6H_5]^+$ and $[M-COC_6H_5-NH_3]^+$ ions on the number of CH_2 groups between the two nitrogen atoms in *N,N'*-dibenzoylated α,ω-alkanediamines (from 70 eV mass spectra; see Ref. [8]). The abundance refers to the total ion current Σ, which has been counted only from $m/e = 120$, so as to eliminate the intense signal at $m/e = 105$ ($[C_6H_5CO]^+$) in all spectra.

of the $[M-acyl]^+$ ions; this is especially strong in compounds with five or six CH_2 groups. The secondary reaction concerned is the elimination of ammonia.

2.2. Loss of Ammonia or Amine from $[M-acyl]^+$ Ions

In the spectrum of *N,N'*-tetramethylenediacetamide *(2)* (Fig. 2) a signal is registered at $m/e = 112$ *[(2b)*, $C_6H_{10}NO$]. Metastable signals indicate that the corresponding ion results from the $[M-COCH_3]^+$ ion [$m/e = 129$, *(2a)*, $C_6H_{13}N_2O$], *i.e. (2a)* loses NH_3. The loss of NH_3 is followed by elimination of ketene and subsequent formation of the ion *(2c)* ($m/e = 70$) (see Scheme 1)[8]. Deuteration experiments have confirmed that the three hydrogen atoms of ammonia derive from the two NH groups and from the α-position of the amide.

Analogous reactions have also been observed in the homologs of *(2)*. The abundances of the corresponding signals are given in Figures 5 and 6, which afford confirmatory evidence of the elimination of ammonia in diacetylated α,ω-alkanediamines with four to seven CH_2 groups. The spectra of compounds containing a larger number of chain members, are void of signals that would be indicative of this type of fragmentation.

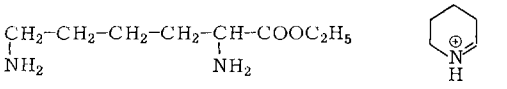
These results would indicate that ion *(2b)* should be cyclic, because its abundance depends on the number of ring members. Acyl cleavage, on the other hand, only proceeds *via* a cyclic transition state (transference of the α-hydrogen to the opposite nitrogen) and is therefore not strongly dependent on the number of ring members. Since *(2b)* is formed from *(2a)*, it is understandable that the abundance (that is, so to say, the concentration) of *(2a)* and its homologous ions is lower (four to seven chain members) if a consecutive reaction leading to *(2b)* or its homologous ions is possible[*].

In the case of trisubstituted tetramethylenediamines the cleavage of a primary amine from the $[M-acyl]^+$ ion is observed instead of the loss of NH_3[8]. Tetrasubstituted tetramethylenediamine derivatives behave differently. Although a large proportion of $[M-acyl]^+$ ions exist, the resulting $[M-acyl-amine]^+$ signals are very weak.

[*] An additional effect can be expected from ions with an eight or nine membered transition state (medium-sized rings) in which, by expulsion of the central hydrogen atoms, the $[M-acyl]^+$ reaction is less favored.

In tetrasubstituted tetramethylenediamine derivatives, instead of NH_3 (as in the *N,N'*-disubstituted amines), a secondary amine should be ejected. This would involve a migration of a radical from one nitrogen atom to the other. It has been demonstrated by deuteration experiments that this reaction does not take place but alternative ones of a completely different nature[16].

The elimination of ammonia from a diamine cation by means of mass spectral fragmentation was first discovered in the case of lysine. The base peak in the spectrum of the ethyl ester of lysine *(6)* is $m/e = 84$; the structure *(6a)* has been proposed

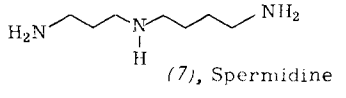


(6) *(6a) ≡ (15c)* (m/e = 84)

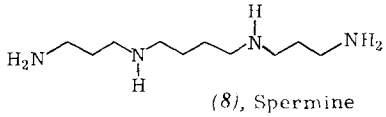
for the corresponding ion[17]. Tagging experiments have proved that both nitrogen atoms can be ejected in the expulsion of NH_3 from the $[M-COOC_2H_5]^+$ ion. A similar decomposition reaction has been postulated[18] for the fragmentation of the ethyl ester of putreanine ($H_2N-(CH_2)_4-NH-(CH_2)_2COOC_2H_5$).

2.3. Trimethylenediamine Derivatives

Regarding nitrogen-nitrogen interaction, substances which derive from trimethylenediamine, *e.g.* spermidine *(7)* or spermine *(8)*, are of special interest. The mass spectra of *N*-acetylated trimethylenediamine derivatives are easy to interpret; moreover, the strong polar compounds *(7)* and *(8)* are better to vaporize in an acetylated state in the mass spectrometer than free amines.



(7), Spermidine



(8), Spermine

N,N',N''-triacetyl-*N*-pentylspermidine *(9)* (Fig. 7) is given as an example to demonstrate the fragmentation behavior of this class of compounds[19]. Remarkable in the mass spectrum of this compound is the severe loss of 43 amu ($COCH_3$) from the molecular ion and the two triads $m/e = 100$, 114, 126 and 143, 157, 169. Regarding the mode of formation of the latter, the triad with lower mass numbers corresponds entirely to the other, so only the one with higher mass numbers will be discussed in the following section.

The three ions with $m/e = 143$, 157 and 169 owe their existence exclusively to the fragmentation of the trimethylenediamine unit and not to that of the tetramethylenediamine part. The following decomposition paths have been derived by means of high resolution spectra, spectra of deuterated and other derivatives, as well as by metastable transitions[19].

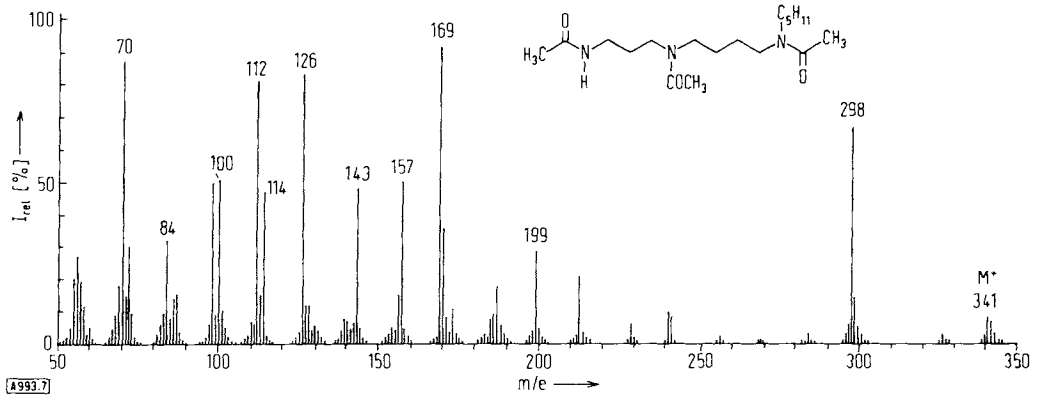
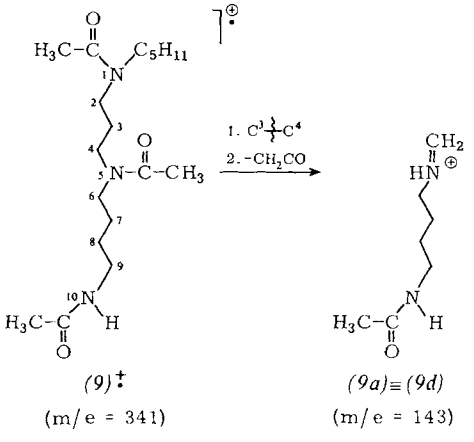


Fig. 7. Mass spectrum of *N,N',N''*-triacetyl-*N*-pentylspermidine *(9)* (see Ref. [19]).

Two mechanisms have been deduced for the formation of the ion $m/e = 143$: α-cleavage to N^5 between C^3 and C^4, followed by the loss of ketene, leads to *(9a)* ($m/e = 143$) (Scheme 2). In addition to this conventional fragmentation there exists a second possible process of formation, initiated by a nitrogen-nitrogen interaction (Scheme 3).



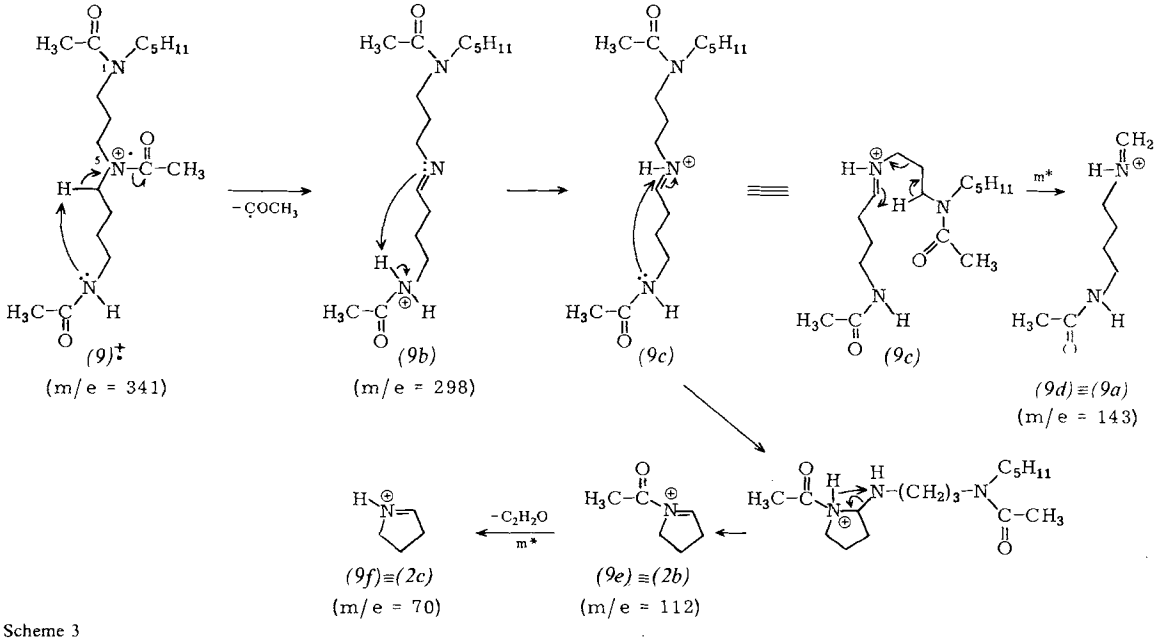
Scheme 2

In the first reaction step the acetyl group splits off from the central nitrogen atom with participation of N^{10} and with shifting of one H from C^6 to N^{10} [*(9b)*, $m/e = 298$]. In the following step this hydrogen atom is transferred to N^5 *(9c)*. Finally, *(9d)* ($m/e = 143$) is formed by a McLafferty-like reaction involving the atoms 2 to 6. In addition, starting from *(9c)*, the ions *(9e)* ($m/e = 112$) and *(9f)* ($m/e = 70$) can be formed in accordance with the reaction sequence demonstrated in Scheme 3 and analogously to the decomposition of *N,N'*-tetramethylenediacetamide *(2)* (Scheme 1).

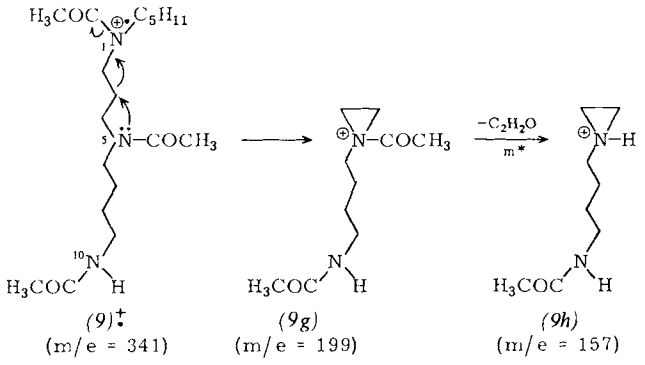
The shifts in the spectrum of the deuterated derivatives favor the structure *(9h)* ($m/e = 157$). It may be assumed that the reaction in this case also is initiated by loss of an *N*-acetyl group (cf. Scheme 4).

The ion of mass $m/e = 169$ can also be formed in two different ways: multiple interference of the nitrogen atoms 5 and 1 leads to formation of *(9l)* ($m/e = 169$), hydrogen atoms being shifted from positions 3 and 4 (Scheme 5). A similar reaction path likewise leads from *(9i)* to *(9l)* (Scheme 6).

The fragmentation of *N,N',N'',N'''*-tetraacetylspermine *(10)* is in agreement with the formulation of the ions 143, 157 and 169 and the proposed routes of formation[13]. Owing to the larger substituent [replacement of the hydrogen atom



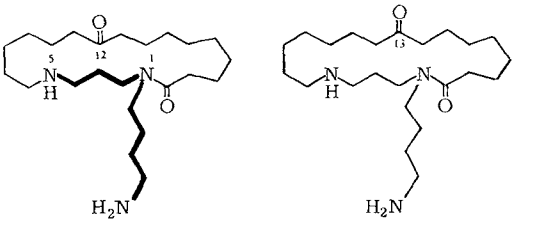
Scheme 3



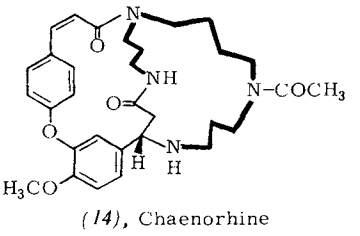
(9)⁺· (m/e = 341) (9g) (m/e = 199) (9h) (m/e = 157)

Scheme 4

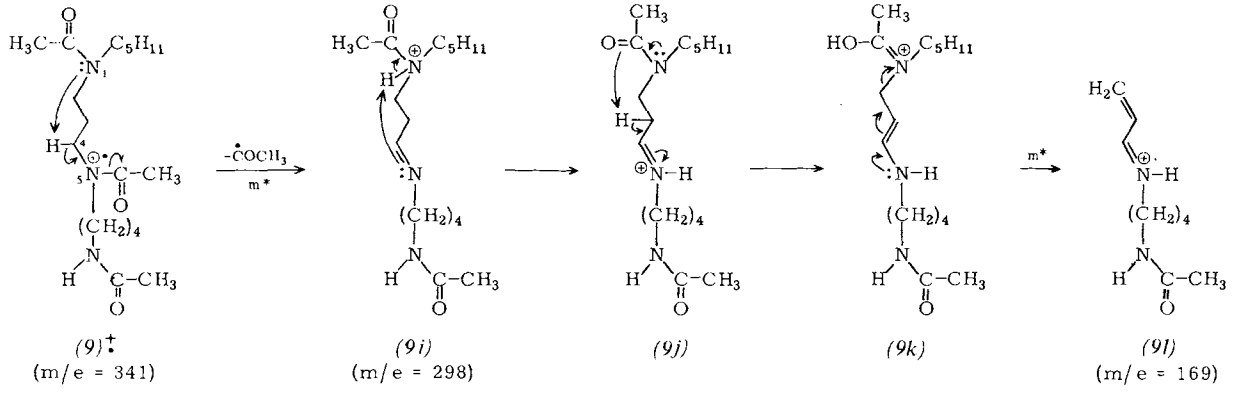
at N^1 by $-(CH_2)_3-NH-COCH_3$], the ions of the corresponding triad are registered at $m/e = 242$, 256 and 268 (+99 amu).



(12), Inandenin-12-one (13), Inandenin-13-one



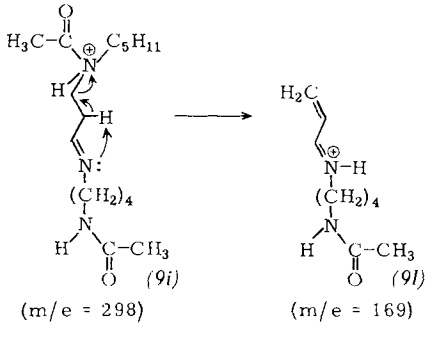
(14), Chaenorhine



(9)⁺· (m/e = 341) (9i) (m/e = 298) (9j) (9k) (9l) (m/e = 169)

Scheme 5

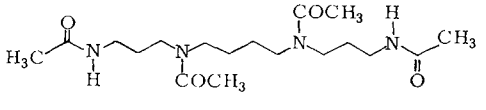
The decomposition of (9)⁺· into (9d) ($m/e = 143$, Scheme 3) requires interaction of all three nitrogen atoms of the molecule. If the nitrogen atom at the end of the tetramethylenedi-



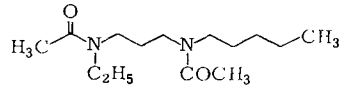
(9i) (m/e = 298) (9l) (m/e = 169)

Scheme 6

amine part is missing, as, *e.g.*, in the compound *N*-ethyl-*N*-pentyl-*N*,*N'*-trimethylenediacetamide (11), the above mentioned triad will still be found (but now shifted to $m/e = 100$, 114, 126), because the "reactive" trimethylenediamine unit is still present; however, as expected, a signal corresponding to (9d) will no longer occur [an ion corresponding to (9a)—caused by conventional fragmentation—is also formed][20].



(10)



(11)

If an *N*-acetylated spermidine or spermine unit is incorporated in a larger molecular structure, the characteristic fragmentation pattern, discussed above, remains unchanged [cf. *e.g.* the discussion of the mass spectra of the alkaloids inandenine and chaenorhine (14)[14], and especially their derivatives (12) and (13)[21]]. This provides a valuable tool for the analysis of unknown alkaloids containing spermidine (7) or spermine (8) as structural elements[12] (cf. also Ref.[22]).

2.4. Mass Spectral S_Ni Reactions[23]

These fragmentation processes, earlier called mass spectral S_N2-like reactions, were first observed[23] in a derivative of the spermidine alkaloid oncinotine (17)[24].

If in an aliphatic, difunctional molecule the charge is localized at a heteroatom, *e.g.* by means of a favored α-fission, a second functional group can attack the carbon atom in the α-position to the charge-carrying heteroatom. During this reaction the charge is taken over by the second functional group and the former charge-carrying group is ejected as a neutral particle.

The spectrum of the 2-ethylpiperidine derivative (15) (Fig. 8, Scheme 7) may be discussed as an example. As expected,

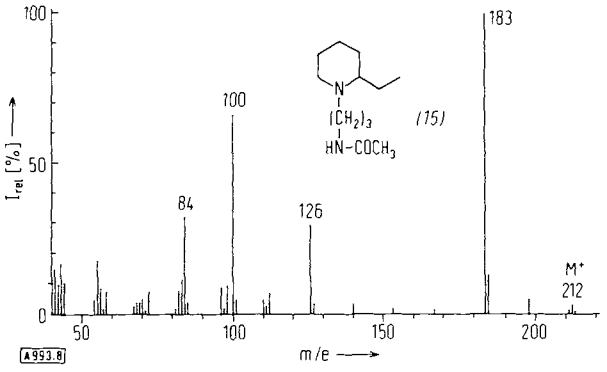
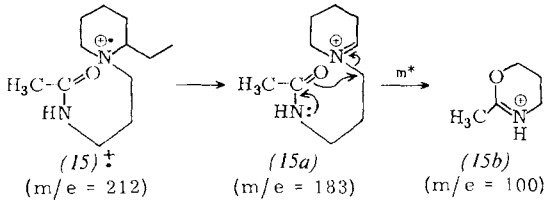


Fig. 8. Mass spectrum of *N*-(γ-acetylaminopropyl)-2-ethylpiperidine *(15)* (see Ref. [23]).





(15c)≡*(6a)*
(m/e = 84)

Scheme 7

the molecular ion first splits off $\cdot C_2H_5$ (in the α-position to the ring nitrogen atom) and yields *(15a)* (*m/e*=183), which gives rise to the most intense signal in the spectrum. In the following reaction step piperideine is eliminated as a neutral fraction (m*) and the ion *(15b)* (*m/e*=100) is formed. On the basis of the following arguments, *(15b)* is assumed to have a cyclic structure. If the aliphatic residue attached to the nitrogen of the piperidine ring carries no further functional group, the S_Ni-reaction will not be observed; instead the product of an onium reaction *(15c)* (*m/e*=84) is favored. The abundance of the ion *(15b)* or the analogous ions depends very strongly on the nature of the functional group at the chain end (Table 1).

The cyclic structure of ion *(15b)* has been derived mainly from the mass spectra of the homologous compounds. It can be presumed that the size of the ring in *(15b)* and analogous ions is directly connected with the abundance of the corresponding signals. Hence for a six-membered ring, *i.e.* for *(15b)*, an abundance maximum can be expected, while with a larger number of ring members the abundance should decrease. This behavior has also been proved experimentally (see Table 1). It follows, at least for this type of compound, that *(15b)* and its homologs are very likely to possess cyclic structures.

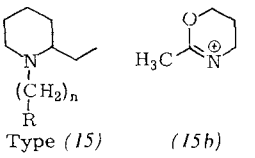
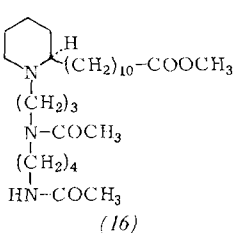


Table 1. Dependence of the abundance (*I*) of the ions analogous and homologous to ion *(15b)* on the nature of the functional group and the number *n* of methylene groups in compounds of type *(15)*.

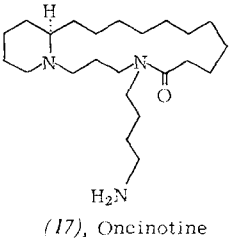
R	*n*	Ring members	Cyclic ion, Type *(15b)* *m/e*	*I* [% Σ_{30}]
$NHCOCH_3$	3	6	100	14.6 [a]
$CONH_2$	3	6	86	10.7
$COOC_2H_5$	3	6	115	1.7
NH_2	3	6	58	1.4
OH	3	6	59	0
$NHCOCH_3$	2	5	86	5.5
$NHCOCH_3$	3	6	100	14.6 [a]
$NHCOCH_3$	4	7	114	2.0
$NHCOCH_3$	5	8	128	0.4

[a] Decomposition of compound *(15)* to ion *(15b)*.

Particularly noteworthy is the fact that a consecutive reaction, in which the ion corresponding to *(15b)* once again enters into such an S_Ni-reaction, has been found to take place[25] in the case of methyl *N*,*N'*-diacetyloncinotinate *(16)*, a degradation product of the natural spermidine alkaloid oncinotine *(17)*[24].



(16)



(17), Oncinotine

It should be emphasized that, in all the cases mentioned above, this decomposition reaction is signified by metastable signals.

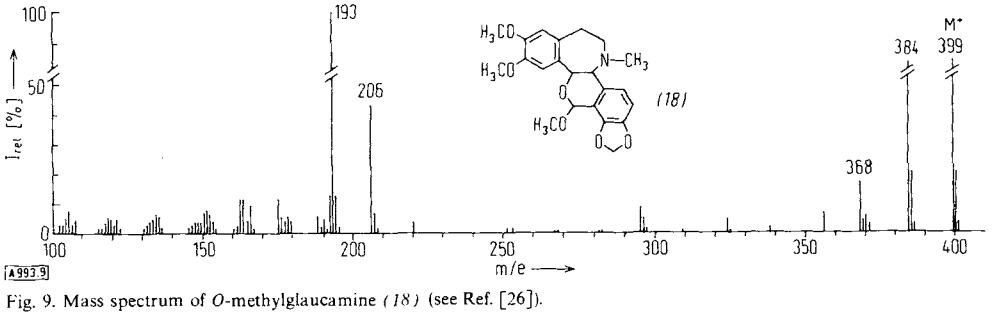
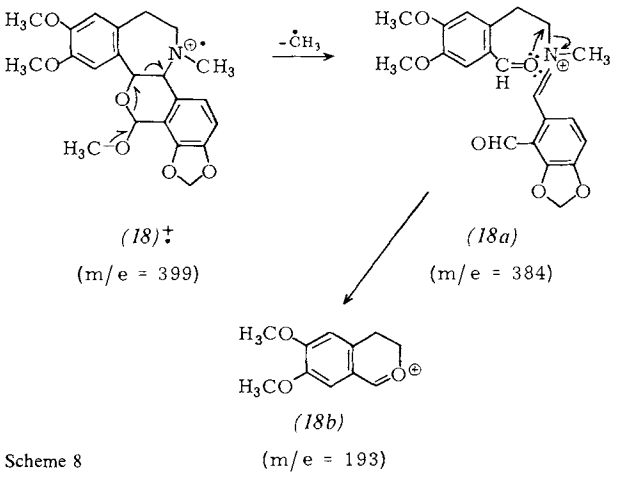


Fig. 9. Mass spectrum of *O*-methylglaucamine *(18)* (see Ref. [26]).

A similar formulation has been used to explain the main fragmentation pattern of the Papaver alkaloid *O*-methylglaucamine *(18)* (Fig. 9)[26]. The base peak is *m/e*=193. The corresponding ion *(18b)* (Scheme 8) derives from the [M−

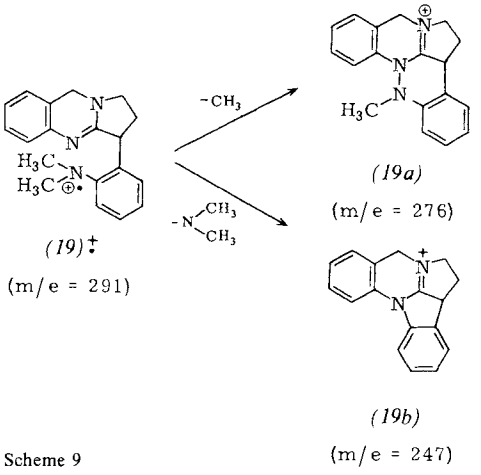
$CH_3]^+$ ion by way of an S_Ni-like fragmentation reaction. This course of decomposition is supported by the spectra of a series of derivatives.



(18)⁺ (m/e = 399) *(18a)* (m/e = 384) *(18b)* (m/e = 193)

Scheme 8

A further fragmentation, which can be explained by the interaction of neighboring nitrogen-containing functional groups, is the cleavage of CH_3 and $N(CH_3)_2$ in the Adhatoda alkaloid vasicoline *(19)* (see Scheme 9) and other, similarly constructed derivatives[27].



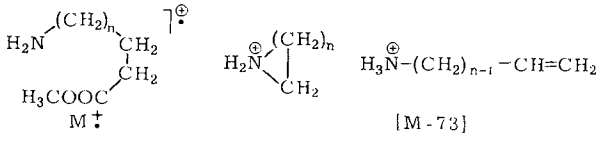
(19)⁺ (m/e = 291) *(19a)* (m/e = 276) *(19b)* (m/e = 247)

Scheme 9

3. Interaction between Nitrogen-containing and Oxygen-containing Functional Groups

As already mentioned in Section 2.4, oxygen-containing functional groups can also interact with amines. The spectra of methyl ω-aminocarboxylates with longer chains show $[M-CH_2COOCH_3]$ ($[M-73]$)[28] as the most abundant peaks in the upper mass range. Signals of these ions also occur, always weaker, in the spectra of aliphatic carboxylic esters (cf. Ref.[29]).

To explain the strong $[M-CH_2COOCH_3]^+$ signal, an interaction between the NH_2 group and the methoxycarbonyl

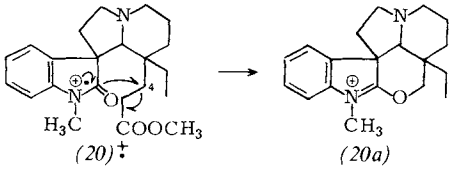


M⁺ [M-73]

group can be presumed and the quoted cyclic structure may be proposed for the corresponding ion[28]. The alternative structure—a primary, unstabilized carbocation—is, for energetic reasons, less likely. It could be possible that, similarly as in the elimination of the *N*-acyl radicals (see Section 2.1), the ejection of $\cdot CH_2COOCH_3$ only occurs with hydrogen migration—this would lead to an alternative structure of an ammonium ion. Unfortunately, in the case of these investigations no references to the influence on the abundance of the $[M-73]^+$ ion as a function of the number of chain members are given. General conclusions cannot therefore be made as yet.

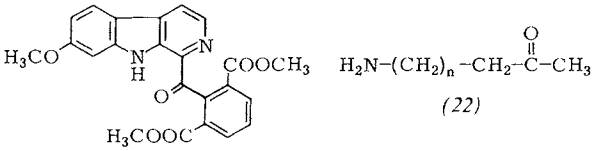
If instead of a methyl ω-amino carboxylate its *N*-acetyl derivatives are examined mass spectrally, the cleavage of the acetyl radical from nitrogen (see Section 2.1) as well as the loss of $\cdot CH_2COOCH_3$ $[M-73]$ from the molecular ion will be observed. Both reactions lose importance as the CH_2 chain becomes longer[8]. The corresponding *N*-benzoyl derivatives behave analogously in the mass spectrometer[8][*].

In this connection reference may be made to the partly unusual fragmentation behavior of the oxindole alkaloid vincatine *(20)*[31]. A characteristic signal is observed in the mass spectrum of this alkaloid at $[M-73]$. High resolution measurements showed that the ion lacks the CH_2COOCH_3 radical. Aliphatic carboxylic acid esters lose, as mentioned above, 73 amu from the molecular ion only to a small extent (cf. Ref.[29]). The unexpected formation of the $[M-73]^+$ ion can be explained by a cyclization to *(20a)*, whereby the oxindole



(20)⁺ (m/e = 370, 100%) *(20a)* (m/e = 297, 20%)

oxygen attacks C^4 with formation of a pyran ring. By way of analogy, the mass spectrum of alstonilidine *(21)*, in which $[M-59]$ is the base peak, would indicate participation of a neighboring group (see[32]) during the decomposition, for the preferred loss of an aromatic methoxycarbonyl group is unusual.



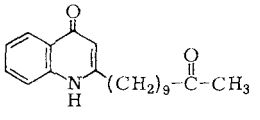
(21), Alstonilidine *(22)*

In the mass spectrometer ω-aminoalkyl methyl ketones of the general formula *(22)* show an intense $[M-57]^+$ signal, which corresponds to the elimination of $\cdot CH_2COCH_3$[33]. Since such a fragmentation behavior is indistinctly or not at all observable in the mass spectral decomposition of mono-

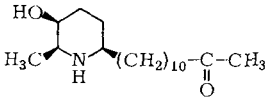
[*] For the mass spectrometric behavior of other ω-amino acid derivatives see Ref. [30].

functional aliphatic ketones, the second functional group must be involved in the formation of this ion.

Similar observations have been made in the decomposition of 2-(10-oxoundecyl)-4-quinolone *(23)*[34] and of cassine *(24)*[35].—Of special interest is the interaction of a tertiary amine and an ethylene acetal group, which are sterically so

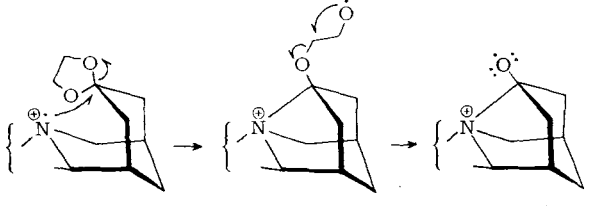


(23)



(24), Cassine

arranged as to favor interaction. Unexpectedly, the mass spectrum of the ethylene acetal of an alkaloid rearrangement product having the partial formula *(25)* does not show the signal of the molecular ion, but that of the amino semiacetal *(25a)* (or the amino ketone), although the acetal is present (spectroscopic and chemical evidence) (cf. Scheme 10)[36].



(25)$^+$ *(25a)*$^+$

Scheme 10

4. Interaction between Oxygen-containing Functional Groups

As demonstrated in Section 2, the mass spectral fragmentation pattern of disubstituted α,ω-alkanediamines of general formula *(26)* (X=NH_2, NHCOR; X′=NH_2, NHCOR, COOR *etc.*) is essentially determined by interaction of the two groups X and X′. Nitrogen-containing groups can be replaced by those containing oxygen, which show a more or less distinct interaction, depending on the type of functional group.

$X-(CH_2)_n-X'$ *(26)*

4.1. Methyl Hydroxy- and Methoxycarboxylates[37]

Figure 10 shows the mass spectrum of methyl 12-hydroxystearate *(27)*[37]. The two characteristic abundant signals at *m/e*=200 and 197 do not occur with comparable intensity in the mass spectrum of methyl stearate[29] and in the spectra of *n*-alkanes containing a central hydroxy group[29]. Nor can their appearance be explained from the spectra of corresponding monofunctional compounds. Consequently, other interpretations have been suggested[37].

The mechanism given in Scheme 11 is supported by metastable signals, spectra of homologous compounds and the spectrum of deuterated derivatives, *e.g.* O—D-*(27)*: The H attached to O is transferred to the carbonyl oxygen before α-fission to the hydroxyl group takes place [*(27a)*]. In the subsequent radical termination process, *(27c)* (*m/e*=229) as well as *(27b)* (*m/e*=200) are formed. The ion *(27c)* loses CH_3OH and is thereby transformed into *(27d)* (*m/e*=197). By deuterium labeling [O—D-*(27)*], it could be demonstrated that the hydrogen atom that splits off with the CH_3OH originates from the OH group. The size of the cyclic transition state ion necessary for this H-transfer has no significant influence on the abundance of these fragment ions. Analogous observations

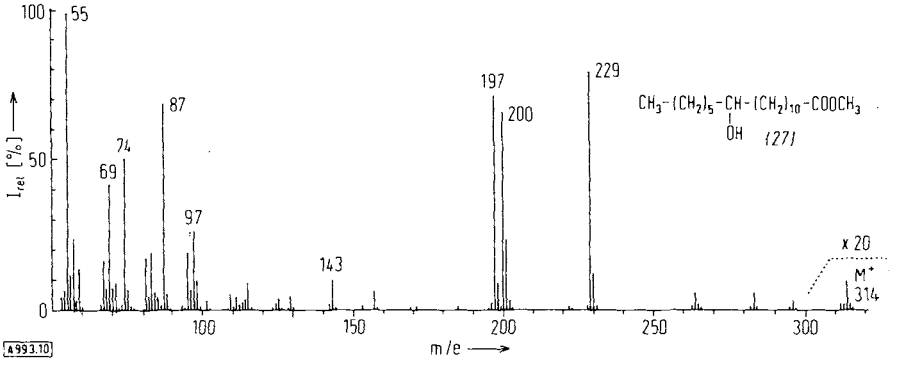
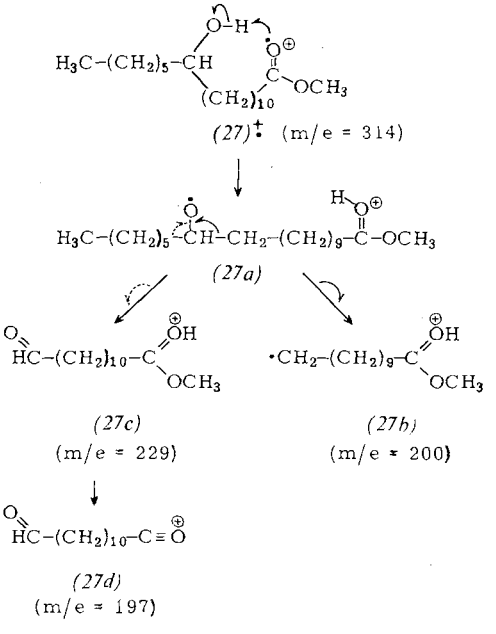


Fig. 10. Mass spectrum of methyl 12-hydroxystearate *(27)* (see Ref. [37]).



(27)$^+$ (m/e = 314)

(27a)

(27c) (m/e = 229)

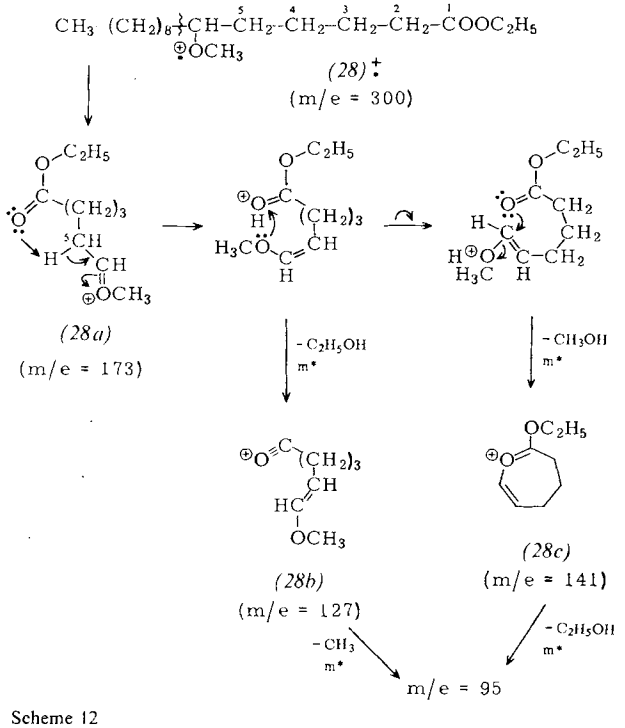
(27b) (m/e = 200)

(27d) (m/e = 197)

Scheme 11

have been made in the elimination of acetyl from acetylated α,ω-alkanediamines (see Section 2.1).

Such interactions also occur in the mass spectral decomposition of *O*-methylated ethyl carboxylates, *e.g.* *(28)*[38]. In the case of *(28)* the exceptional decomposition shown in Scheme 12, which is evidenced by metastable signals, has been confirm-

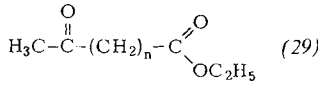


Scheme 12

ed: The ion of mass number 173 [*(28a)*], formed by an α-cleavage to the methoxy group, is first converted by loss of CH_3OH into *(28c)* (*m/e* = 141) and then by loss of C_2H_5OH into *m/e* = 95. The reciprocal process [*(28a)* $-C_2H_5OH \rightarrow$ *(28b)* $-CH_3OH \rightarrow$ (*m/e* = 95)] is shown by metastable signals. As has been demonstrated by deuteration experiments, the additional hydrogen atom required in the removal of CH_3OH or C_2H_5OH, originates from position 5 of the compound. The mechanism, mentioned in Scheme 12, can be discussed analogously to the elimination of NH_3 from the $[M-R]^+$ ions in acetylated α,ω-diamines (see Section 2.2). The subsequent reactions of ions *(28b)* and *(28c)* to give *m/e* = 95, have not been completely explained by the deuteration experiments carried out so far[38].

4.2. Ketocarboxylic Acid Esters

The ketocarboxylic acid esters of general formula *(29)*[39] demonstrate most clearly the interaction effects in mass spectral decomposition processes. The spectrum of ethyl 7-oxooc-



(29)

tanoate *(30)* measured at 70 and 12 eV is shown in Fig. 11. All the intense signals, excepting the signal at *m/e* = 129, can be explained on the basis of the spectra of the corresponding monofunctional alkanes[29,40,41]. The ion of mass

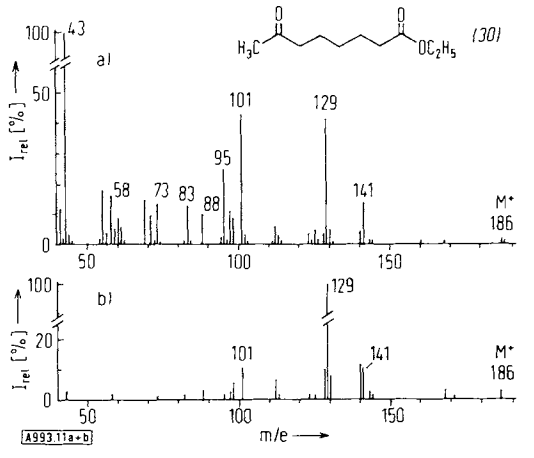
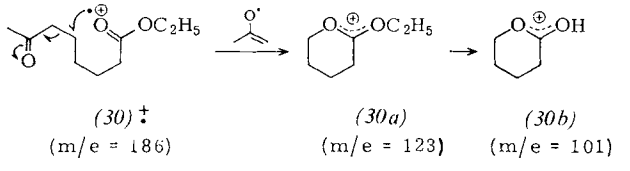


Fig. 11. Mass spectrum of ethyl 7-oxooctanoate *(30)*: a) at 70 eV, b) at 12 eV (see Ref. [39]).

number 129 corresponds to the loss of 57 amu (C_3H_5O) from the molecular ion. An analogous reaction can be observed with amino ketones (see Section 3).

A decomposition mechanism leading to a cyclic ion (Scheme 13) is assumed in the case of the ketocarboxylates of type *(29)*. In the case of compound *(30)* the structure *(30a)*



Scheme 13

with a six-membered ring[*] is suggested for the ion $[M-57]^+$. To confirm the cyclic nature of this ion, the mass spectra of homologous ethyl ketocarboxylates have been investigated (see Fig. 12).

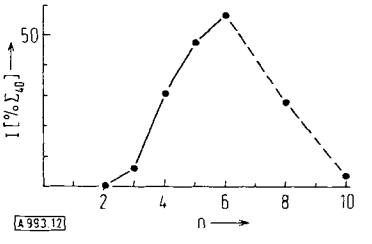


Fig. 12. Dependence of the abundances of $[M-57]^+$ ions on the number *n* of the CH_2 groups between the keto- and ethoxycarbonyl group in ketocarboxylates of type *(29)* at 12 eV (see Ref. [39]). The number of ring members in the $[M-57]^+$ ion is *n* + 1.

The $[M-57]^+$ signal is most intense in compounds that are able to form a five-, six- or seven-membered ring. The tendency to form smaller or larger rings is much less or even negligible.

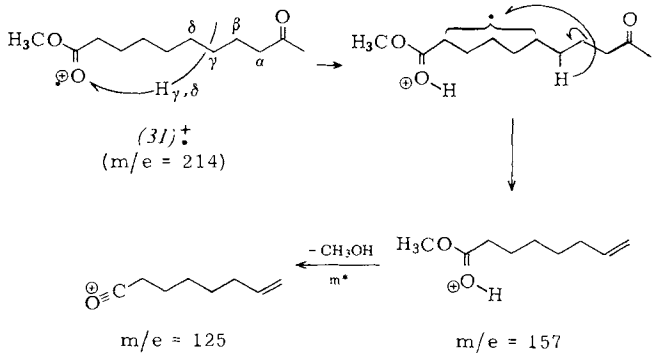
These results agree with those obtained in the fragmentation of *N*,*N*′-dibenzoylated[8] and *N*,*N*′-diacetylated α,ω-alkanediamines[8] and of *N*-(ω-acetylaminoalkyl)-2-ethylpiperidines[23] to cyclic ions (see Section 2).

[*] It seems that the signal at *m/e* = 101 derives from *(30a)*. A proposed structure is *(30b)*. In the spectrum of the corresponding methyl ketocarboxylate this signal is missing [39].

On comparing the spectra of *(30)* at 70 and 12 eV (Fig. 11), it is striking how the intensity of the $[M-57]^+$ signal markedly increases, while at the same time the ionization voltage decreases. This proves that a lesser amount of energy is needed for such molecular rearrangements than for the competition reactions.

The *O*-acetyl derivatives of ω-hydroxy methyl ketones[39] behave similarly to the ketocarboxylates of type *(29)*. An abundance maximum corresponding to that of the $[M-57]^+$ ions in Figure 12 can also be observed in these compounds, in which the ion, formed by interaction, contains a five- or six-membered ring.

The mass spectrometric decomposition of methyl 10-oxoundecanoate *(31)* has recently been thoroughly studied regarding the loss of 57 amu [$m/e=157$] and resultant cleavage of CH_3OH ($m/e=125$) and CO ($m/e=97$) (m*, deuteration, high resolution data)[42]. On the basis of the D-distribution in the daughter ion $m/e=125$, the following reaction course is suggested:



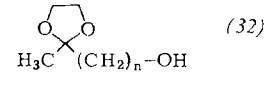
Scheme 14

Compound *(31)* decomposes (Scheme 14) in a completely different fashion to that of *(30)* (Scheme 13), although these compounds represent methyl and ethyl esters, respectively, of homologous acids. The homologous series of the methyl esters have not yet been investigated in detail.

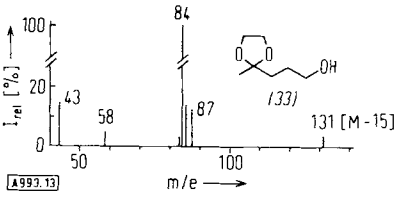
It can hardly be presumed that the decomposition reactions are strongly influenced by the nature of the alcohol groups, although in the case of the ethyl ester the onium reaction [loss of C_2H_4 from *(30a)* to *(30b)*] is dominant. Probably it is the difference in chain length of the compounds investigated which is responsible for the different fragmentation paths. The possibility that both mechanisms are correct and that their predominance varies according to the distance between the two functional groups, cannot be ruled out.

4.3. Hydroxyethylene Acetals

Another very illustrative example concerning the interaction of oxygen-containing functional groups in mass spectral fragmentations has been discovered in ethylene acetals of type *(32)*[39]. Mass spectra of ethylene acetals are generally distinguished by intense fragment ion signals resulting from α-cleavages to the acetal oxygen atoms[41,43]. The signals at $[M-(CH_2)_n-OH]^+$ and $[M-15]^+$ in the spectra of the compounds of type *(32)* derive from such processes. The $[M-62]^+$ signals, however, are caused by interaction between the acetal and hydroxy groups (see Fig. 13).



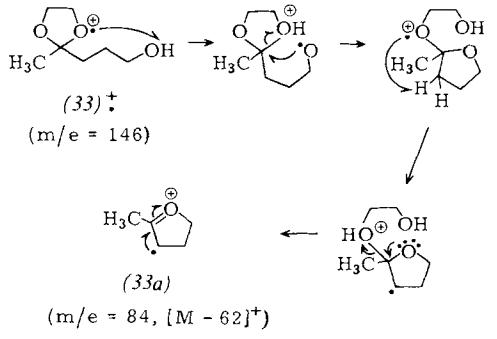
(32)



(33)

Fig. 13. Mass spectrum of the ethylene acetal of 3-(2-methyl-1,3-dioxolan-2-yl)propan-1-ol *(33)* at 12 eV (see Ref. [39]).

The mechanism for the fragmentation of *(33)*, according to the result so far obtained, is outlined in Scheme 15. It is supported by deuteration experiments and by spectra of model



Scheme 15

substances (*e.g.* propylene acetals)[39]. The abundance of the $[M-62]^+$ ion in this type of fragmentation also depends on the size of the ring. Once again the abundance maximum occurs in the case of five- and six-membered rings.—Ions formed by difunctional interaction have also been recorded in the mass spectra of ethylene acetals of ketocarboxylates[39].

4.4. Dicarboxylic Acid Diesters

As expected dimethyl dicarboxylates of straight-chain hydrocarbons also belong to those compounds whose fragmentation is at least partly determined by interaction of the functional groups.

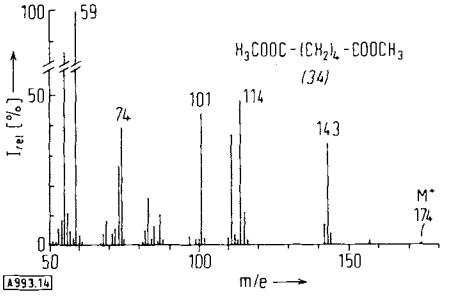


Fig. 14. Mass spectrum of dimethyl adipate at 70 eV (see Ref. [29]).

Regarding difunctional interaction, one signal is of special importance: $m/e=101$ $[M-73]^+$.

Cleavage of 73 atomic mass units corresponds to the loss of $\cdot CH_2COOCH_3$ from the molecular ion. Such a fragmenta-

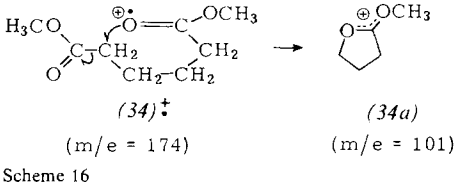
tion is registered only to a very small degree in methyl monocarboxylates (see Section 3)[29]; yet in dimethyl dicarboxylates it can give rise to one of the highest peaks in the spectrum. The values found in the homologous series of these compounds are listed in Table 2. It will be noticed that the most abundant signal occurs in dicarboxylic acids with four or five CH_2 groups. This would indicate, in analogy with the cyclization

Table 2. Dependence of the abundance (I) of the $[M-73]^+$ signal in the spectra of homologous dicarboxylic acid dimethyl esters on the number n of the methylene groups (data from [29]).

$H_3COOC-(CH_2)_n-COOCH_3$

	n	$[M]^+$ m/e	$[M-73]^+$ m/e	$I_{rel.}$ [%]	I[% Σ_{50}]
	2	146	73	1	0.03
	3	160	87	16	4.37
(34)	4	174	101	44	7.68
	5	188	115	79	9.11
	6	202	129	58	1.45
	7	216	143	28	3.30

reactions discussed above, that cyclic ions are probably also formed here. To explain the fragmentation pattern, the reaction course outlined in Scheme 16 has been suggested[39]. Accordingly, the $[M-73]^+$ signals are most abundant with ions of five- or six-membered rings [type *(34a)*]. Other esters of dicarboxylic acids behave similarly to the dimethyl esters.



(34)$^+$ (m/e = 174) *(34a)* (m/e = 101)

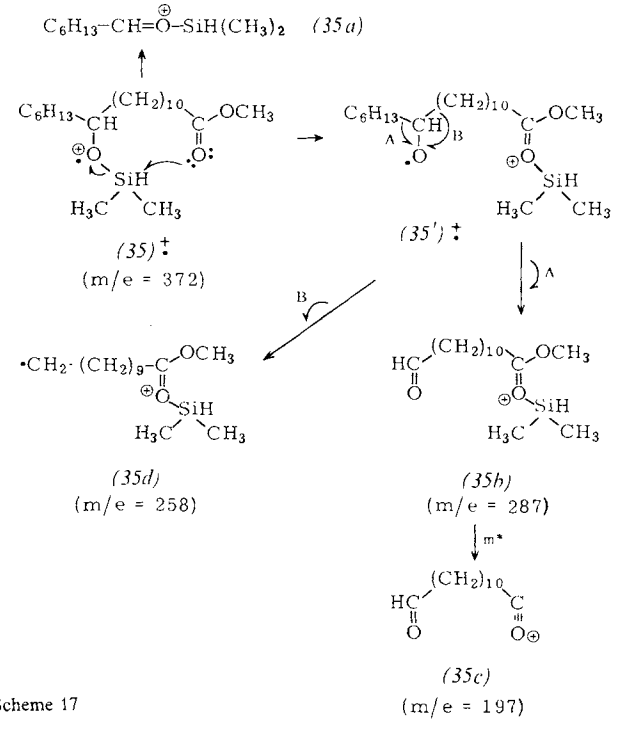
Scheme 16

Interactions of the type discussed in this section can also occur in other compounds having oxygen-containing functional groups: α,α'-disubstituted tetrahydrofuran derivatives[44], diketones[45], hydroxycyclohexanones[46], hydroxybenzyl ethers[47], hydroxylalkyl ethers[47], α,δ-diols[48] (cf. also the discussion on the fragmentation mechanisms of aporphine alkaloids[49]).

5. Interaction between Silicon- and Oxygen-containing Functional Groups

The mass spectral decomposition of the dimethylsilyl ether of methyl 12-hydroxyoctadecanoate *(35)* (Fig. 15), just like that of the trimethylsilyl ether, involves interfunctional interactions[50]. Hence compound *(35)* behaves analogously to the hydroxycarboxylic acid esters[37] (Section 4.1).

The main fragment ions in the spectra of *(35)*, *(35a)* ($m/e=173$) and *(35b)* ($m/e=287$) correspond to the α-cleavages to the dimethylsiloxy group. The subsequent reactions of these ions include interaction of neighboring groups; some of these are shown in Scheme 17.—During the fragmentation, the dimethylsilyl radical migrates from the alcoholic to the ester function. This can be deduced from the fact that ion *(35b)* is transformed into *(35c)* *via* elimination of $C_3H_{10}OSi$. This is also proved by the occurrence of a metastable signal, by high resolution data, and by spectra of deuterated compounds (trideuteriomethyl 12-dimethylsiloxyoctadecanoate, 12-D- and 2,2-D_2-derivatives). If the 11,12 bond in the isomeric molecular ion *(35')*$^+$ is broken, ion *(35d)* results, which transforms by means of further rearrangement reactions into a more stable radical ion. (For similar decomposition reactions see also Ref. [7, 51] and the literature cited in



(35)$^+$ (m/e = 372) *(35')*$^+$ *(35d)* (m/e = 258) *(35b)* (m/e = 287) *(35c)* (m/e = 197)

Scheme 17

Ref. [52].) In the lower part of the mass spectrum of *(35)* further signals occur which are due to ions whose origin can also be traced back to difunctional interaction: $m/e=145$ *(35e)*, 132 *(35f)*, 89 *(35g)*.

In the spectra of α-halo-ω-trimethylsiloxyalkanes *(36)* and trimethylsilyl esters of ω-halo fatty acids *(37)* very intense

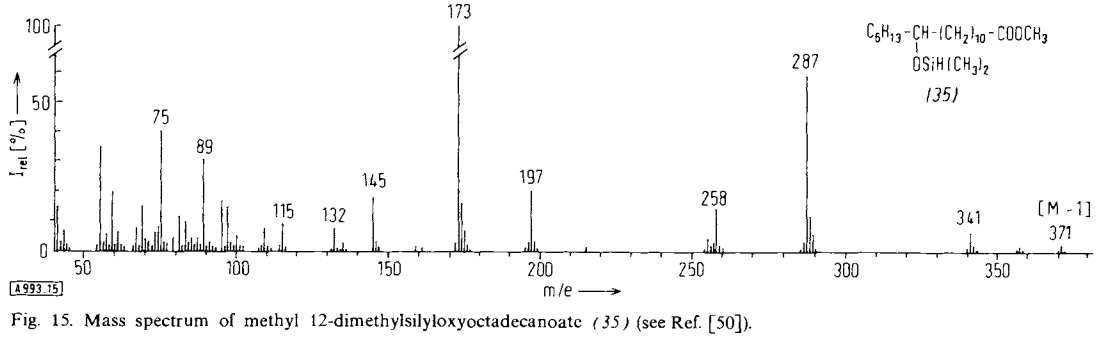
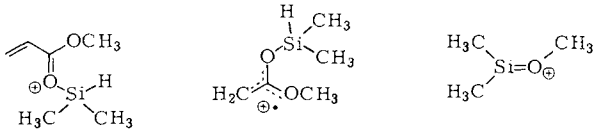
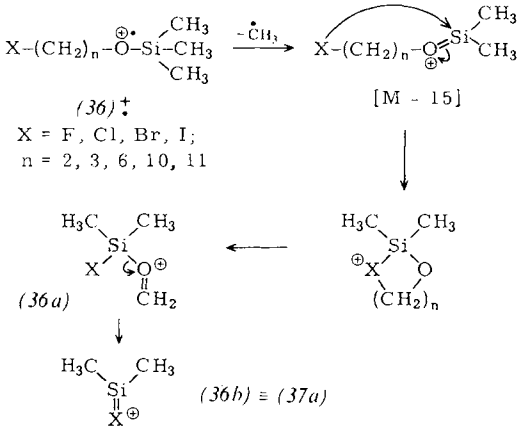


Fig. 15. Mass spectrum of methyl 12-dimethylsilyloxyoctadecanoate *(35)* (see Ref. [50]).



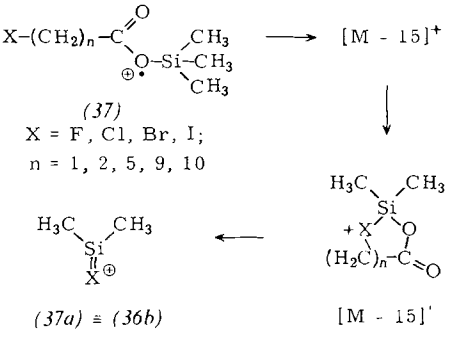
(35e) (m/e = 145) *(35f)* (m/e = 132) *(35g)* (m/e = 89)

ions can partly be observed which are indicative of the involvement of neighboring group participation[52] (see Schemes 18 and 19, respectively).



Scheme 18

It is interesting to note that in compounds of type *(36)* and *(37)* this effect depends on the chain length of the alkane[*].

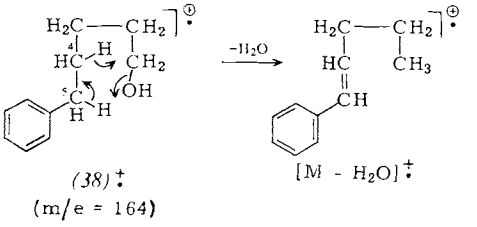


Scheme 19

6. Interaction between Other Functional Groups[53]

In the mass spectrometer 5-phenyl-1-hexanol and, even more distinctly, 5-phenyl-1-pentanol *(38)* lose water from the molecular ion. The main site from which one of the protons is removed is from the benzylic position. In the case of *(38)* 14% of the protons lost originate from position 4 and 75% from position 5. The following has been proposed as being the principal mechanism involved[54] (see Scheme 19a).

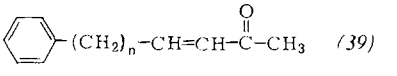
This finding would suggest classification under the group of fragmentations based on an interaction of the functional groups; it is of special importance because a hydrogen atom, activated by the phenyl nucleus, is split off together with another functional group (OH). Unfortunately further investigations, which would allow a generalization of this reaction, are still lacking.



(38)$^{+\cdot}$ (m/e = 164)

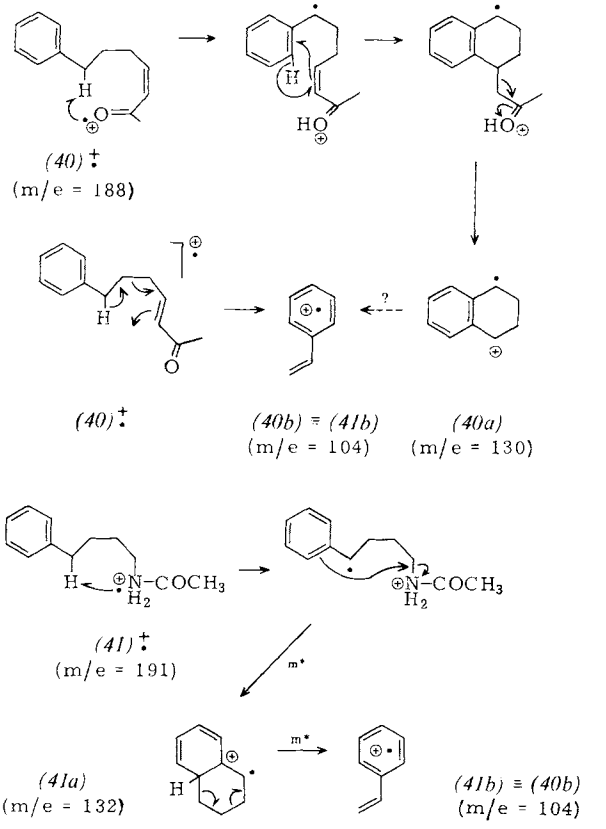
Scheme 19a

A mutual influence of phenyl group and carbonyl function has been proved in the decomposition of phenyl ketones of general formula *(39)*[55].



(39)

The spectrum of 7-phenyl-3-hepten-2-one *(40)* is shown in Fig. 16. Apart from the base peak at $m/e=91$ (tropylium ion)[*] and the signal at $m/e=43$ ($H_3C-C\equiv\overset{\oplus}{O}$), which are also observed in the spectra of the corresponding monofunctional compounds, the other intense signals, *i.e.* those at $m/e=130$, 105, 104, 97[**] and 84, are due to difunctional interactions (cf. Scheme 20). It is noteworthy that the corre-



(40)$^{+\cdot}$ (m/e = 188) *(40b)* ≡ *(41b)* (m/e = 104) *(40a)* (m/e = 130)

(41)$^{+\cdot}$ (m/e = 191) *(41a)* (m/e = 132) *(41b)* ≡ *(40b)* (m/e = 104)

Scheme 20

[*] Difunctional interactions also occur in the mass spectral fragmentation of cycloalkane derivatives [7].

[*] As D-labeling experiments have shown, the formation of $m/e=91$ is of a complex nature and will therefore not be discussed any further in this report (cf. Ref. [55]).

[**] The $[M-91]^+$ ion $m/e=97$ [in the spectrum of *(40)*] could be cyclic.

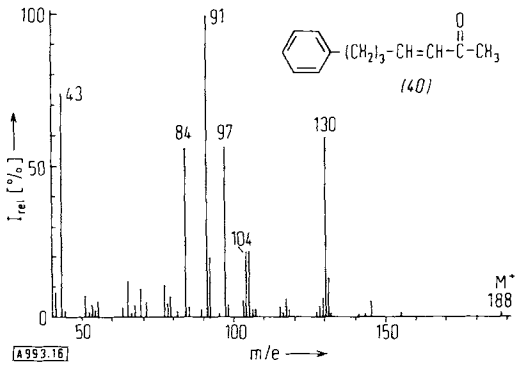


Fig. 16. Mass spectrum of 7-phenyl-3-hepten-2-one *(40)* (see Ref. [55]).

sponding nitrogen compound, *N*-(4-phenylbutyl)acetamide *(41)*, shows a quite similar spectrum (Fig. 17) and consequently

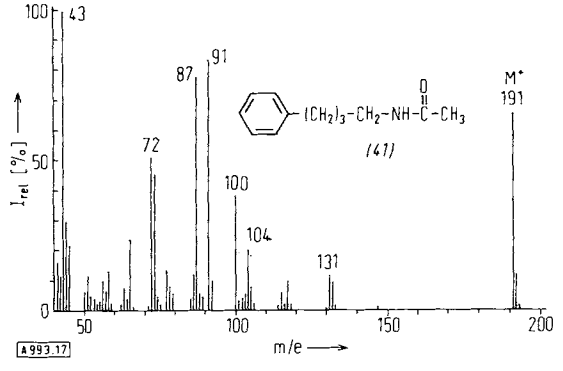


Fig. 17. Mass spectrum of *N*-(4-phenylbutyl)acetamide *(41)* (see Ref. [56]).

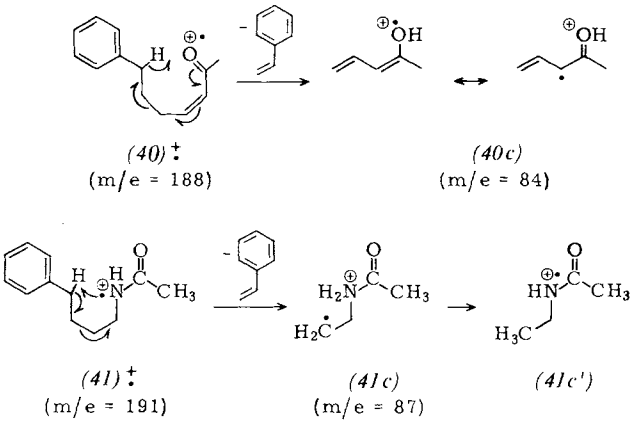
undergoes an analogous decomposition[56]. A comparison with the corresponding monofunctional compounds shows that the occurrence of ions with mass numbers 132, 100, 87 and, to some extent, 104 in the decomposition of *(41)* cannot be explained without considering the effect of a second functional group.

Scheme 20 outlines the formation paths of the ions *(40a)* (*m/e* = 130) and *(40b)* (*m/e* = 104) from *(40)*, and of *(41a)* (*m/e* = 132) and *(41b)* (*m/e* = 104) from *(41)*. In both cases the mode of decomposition has been confirmed by measurements on deuterated compounds. In both examples a benzylic hydrogen atom is transferred to the heteroatom, and the group carrying this heteroatom is then eliminated by cyclization of the molecular residue; *(41a)* loses C_2H_4 (m*) and forms *(41b)*. Whether formation of this ion from *(40)* follows a comparable route, or originates directly from $(40)^{\ddagger}$ by a McLafferty rearrangement, has not yet been investigated. (Experiments with deuterated compounds have shown that the fragmentation to *(41a)*, mentioned in Scheme 20, is the main decomposition reaction.)

The signal at *m/e* = 84 in the spectrum of *(40)* corresponds to that at *m/e* = 87 in the spectrum of *(41)* (see Scheme 21). Both are formed in an analogous manner. Once again, a benzylic hydrogen atom is transferred to the heteroatom and leads to expulsion of styrene as a neutral fragment and formation of *(40c)* and *(41c)* [or *(41c')*] as charged particles.

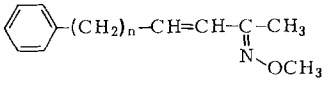
The investigations on the fragmentation reactions of compounds *(40)* and *(41)* are supported by experiments with homologous, analogous and deuterated derivatives[55,56].

A similar mass spectrometric behavior to that mentioned, above for the phenyl ketones of general formula *(39)* is also displayed by their *O*-methyl-substituted oximes[57].



Scheme 21

A larger number of 3-methoxydecanes, each carrying another substituent (I, Br, Cl, OH, SH, SCH_3, NH_2, $N(CH_3)_2$, =O, ethylenedioxy) at C^8, have already been investigated mass spectrometrically[58]. The spectra would suggest that some



difunctional interactions take place during the decomposition processes. However, a detailed knowledge of the modes of decomposition is still lacking, since a closer study of these reactions using deuterated derivatives has so far only been carried out in one case.

7. Conclusion

Our discussion of the above mentioned fragmentations, which are caused by interaction of functional groups during mass spectral decomposition, has purposely been confined to the investigation of substituted alkanes, although this mode of fragmentation also occurs in other classes of substances.

In summarizing these investigations it can be stated that in nearly all the cases discussed above, the decomposition reactions are determined by additional activated positions (α-positions to heteroatoms, benzyl positions or activated hydrogen atoms on heteroatoms) in the molecule. As would be expected, the di- and polyfunctional compounds differ from the corresponding monofunctional compounds regarding such activation; this is clearly expressed in the mass spectra.

As can be seen from the examples mentioned above, our study of mass spectral fragmentations, which are influenced by neighboring groups, or participation of two functional groups, is still in its infancy and it can be assumed that more detailed research will be carried out in this field during the next few years. A detailed knowledge of the mechanisms

of mass spectral fragmentation should not only interest the mass spectroscopist, but also all organic chemists who resort to the use mass spectroscopy as an analytical method. Only by such combined interest can we expect to gain more structural information from the spectra.

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Translated by Barbara Hesse

[1] *K. Biemann:* Mass Spectrometry—Organic Chemical Applications. McGraw-Hill, New York 1962.

[2] *K. Ziegler, H. Eberle,* and *H. Ohlinger,* Liebigs Ann. Chem. *504*, 94 (1933); *M. Stoll* and *A. Rouvé,* Helv. Chim. Acta *17*, 1283 (1934); *Ch. D. Hurd* and *W. H. Saunders,* J. Amer. Chem. Soc. *74*, 5324 (1952).

[3] *G. Spiteller,* Monatsh. Chem. *92*, 1147 (1961); *K. T. Tomer, T. Gebreyesus,* and *C. Djerassi,* Org. Mass Spectrom. *7*, 383 (1973); *J. T. Bursey, M. M. Bursey,* and *D. G. I. Kingston,* Chem. Rev. *73*, 191 (1973); cf. [41], p. 517; *R. T. Coutts* and *J. L. Malicky,* Org. Mass Spectrom. *7*, 985 (1973).

[4] *J. L. Holmes,* Org. Mass Spectrom. *7*, 335 (1973); *F. Benoit, J. L. Holmes,* and *N. S. Isaacs, ibid. 2*, 591 (1969).

[5] *F. Benoit* and *J. L. Holmes,* Org. Mass Spectrom. *6*, 541 (1972).

[6] *F. Benoit* and *J. L. Holmes,* Org. Mass Spectrom. *6*, 549 (1972).

[7] *R. T. Gray, J. Diekman, G. L. Larson, W. K. Musker,* and *C. Djerassi,* Org. Mass Spectrom. *3*, 973 (1970); *P. D. Woodgate, R. T. Gray,* and *C. Djerassi, ibid. 4*, 257 (1970).

[8] *H. J. Veith, A. Guggisberg,* and *M. Hesse,* Helv. Chim. Acta *54*, 653 (1971).

[9] *Z. Pelah, M. A. Kielczewski, J. M. Wilson, M. Ohashi, H. Budzikiewicz,* and *C. Djerassi,* J. Amer. Chem. Soc. *85*, 2470 (1963).

[10] *A. Guggisberg, H. J. Veith,* and *M. Hesse,* Tetrahedron Lett. *1970*, 3639.

[11] *H. J. Veith* and *M. Hesse,* Advan. Mass Spectrom. *5*, 685 (1971).

[12] *A. Guggisberg, R. W. Gray,* and *M. Hesse,* to be published.

[13] *E. Schöpp* and *M. Hesse,* Helv. Chim. Acta *56*, 124 (1973).

[14] *H. O. Bernhard, I. Kompiš, S. Johne, D. Gröger, M. Hesse,* and *H. Schmid,* Helv. Chim. Acta *56*, 1266 (1973).

[15] *K. Watanabe, T. Nakayama,* and *J. Mottl,* J. Quant. Spectrosc. Radiat. Transfer *2*, 369 (1962), cited in *R. C. Weast:* Handbook of Chemistry and Physics. Chemical Rubber 1969—1970, p. E-80.

[16] *F. Pulver* †, planned Diplomarbeit, Universität Zürich.

[17] *K. Biemann, J. Seibl,* and *F. Gapp,* J. Amer. Chem. Soc. *83*, 3795 (1961).

[18] *T. Shiba, I. Kubota,* and *T. Kaneko,* Tetrahedron *26*, 4307 (1970).

[19] *H. Bosshardt, H. J. Veith,* and *M. Hesse,* Org. Mass Spectrom. *6*, 325 (1972).

[20] *E. Lerch* u. *M. Hesse,* Helv. Chim. Acta *55*, 1883 (1972).

[21] *H. J. Veith, M. Hesse,* and *H. Schmid,* Helv. Chim. Acta *53*, 1355 (1970).

[22] *G. Englert, K. Klinga, Raymond-Hamet, E. Schlittler,* and *W. Vetter,* Helv. Chim. Acta *56*, 474 (1973).

[23] *K. Sailer* and *M. Hesse,* Helv. Chim. Acta *51*, 1817 (1968).

[24] *M. M. Badawi, A. Guggisberg, P. van den Broek, M. Hesse,* and *H. Schmid,* Helv. Chim. Acta *51*, 1813 (1968); *M. M. Badawi, K. Bernauer, P. van den Broek, D. Gröger, A. Guggisberg, S. Johne, I. Kompiš, F. Schneider, H.-J. Veith, M. Hesse,* and *H. Schmid,* Pure Appl. Chem. *33*, 81 (1973).

[25] *M. Hesse,* Chimia *24*, 21 (1970).

[26] *J. Slavík, L. Dolejš, K. Vokáč,* and *V. Hanuš,* Collect. Czech. Chem. Commun. *30*, 2864 (1965).

[27] *S. Johne, D. Gröger,* and *M. Hesse,* Helv. Chim. Acta *54*, 826 (1971).

[28] *R. S. Wolff* and *A. Caspar,* Tetrahedron Lett. *1970*, 1807.

[29] *E. Stenhagen, S. Abrahamsson,* and *F. W. McLafferty:* Atlas of Mass Spectral Data. Interscience, New York 1969, Vol. 1—3.

[30] *S. Osman, P. Hoagland,* and *C. J. Dooley,* Org. Mass Spectrom. *7*, 1083 (1973).

[31] *W. Döpke, H. Meisel,* and *H.-W. Fehlhaber,* Tetrahedron Lett. *1969*, 1701.

[32] *W. D. Crow, N. C. Hancox, S. R. Johns,* and *J. A. Lamberton,* Aust. J. Chem. *23*, 2489 (1970); *M. Hesse:* Progress in Mass Spectrometry. 1: Indolalkaloide. Verlag Chemie, Weinheim 1974.

[33] *R. J. Highet* and *P. F. Highet,* Tetrahedron Lett. *1970*, 1803.

[34] *C. Kan-Fan, B. C. Das, P. Boiteau,* and *P. Potier,* Phytochemistry *9*, 1283 (1970).

[35] *D. Lythgoe* and *M. J. Vernenge,* Tetrahedron Lett. *1967*, 1133.

[36] *Y. Morita,* Universität Zürich, unpublished results.

[37] *R. E. Wolff, M. Greff,* and *J. A. McCloskey,* Advan. Mass Spectrom. *4*, 193 (1968).

[38] *M. Greff, R. E. Wolff, G. H. Draffan,* and *J. A. McCloskey,* Org. Mass Spectrom. *3*, 399 (1970).

[39] *J. R. Dias* and *C. Djerassi,* Org. Mass Spectrom. *6*, 385 (1972).

[40] *G. Spiteller:* Massenspektrometrische Strukturanalyse organischer Verbindungen. Verlag Chemie, Weinheim 1966.

[41] *H. Budzikiewicz, C. Djerassi,* and *D. H. Williams:* Mass Spectrometry of Organic Compounds. Holden-Day, San Francisco 1967.

[42] *W. J. Richter* and *J. G. Liehr,* Helv. Chim. Acta *55*, 2421 (1972).

[43] *H. Audier, A. Diara, M. de J. Durazo, M. Fetizon, P. Foy,* and *W. Vetter,* Bull. Soc. Chim. Fr. *1963*, 2827.

[44] *R. Brandt* and *C. Djerassi,* Helv. Chim. Acta *51*, 1750 (1968).

[45] *J. Kossanyi* and *J. K. Mogto,* Org. Mass Spectrom. *3*, 721 (1970).

[46] *M. M. Green, D. S. Weinberg,* and *C. Djerassi,* J. Amer. Chem. Soc. *88*, 3883 (1966).

[47] *M. Sheehan, R. J. Spangler,* and *C. Djerassi,* J. Org. Chem. *36*, 3526 (1971).

[48] *G. Horváth* and *J. Kuszmann,* Org. Mass Spectrom. *6*, 447 (1972).

[49] *M. Ohashi, J. M. Wilson, H. Budzikiewicz, M. Shamma, W. A. Slusarchyk,* and *C. Djerassi,* J. Amer. Chem. Soc. *85*, 2807 (1963); *A. H. Jackson* and *J. A. Martin,* J. Chem. Soc. *C 1966*, 2181.

[50] *D. H. Hunneman* and *W. J. Richter,* Org. Mass Spectrom. *6*, 909 (1972).

[51] *D. H. Hunneman* and *G. Eglinton,* Phytochemistry *11*, 1989 (1972).

[52] *E. White* and *J. A. McCloskey,* J. Org. Chem. *35*, 4241 (1970).

[53] Cf. also *I. Howe* and *D. H. Williams,* J. Amer. Chem. Soc. *90*, 5461 (1968).

[54] *S. Meyerson* and *L. C. Leitch,* Advan. Mass Spectrom. *5*, 659 (1971); J. Amer. Chem. Soc. *93*, 2244 (1971).

[55] *R. J. Liedtke, A. F. Gerrard, J. Diekman,* and *C. Djerassi,* J. Org. Chem. *37*, 776 (1972).

[56] *R. Wild* and *M. Hesse,* Helv. Chim. Acta *57*, 452 (1974); cf. also *E. Hefti,* Diplomarbeit, Universität Zürich 1971.

[57] *R. J. Liedtke, Y. M. Sheikh, A. M. Duffield,* and *C. Djerassi,* Org. Mass Spectrom. *6*, 1271 (1972).

[58] *G. Remberg* and *G. Spiteller,* Chem. Ber. *103*, 3640 (1970).

A Convenient Procedure for the Synthesis of Cyclobutanones[**]

By *Abdul Sidani, Jacqueline Marchand-Brynaert,* and *Léon Ghosez*[*]

We have previously reported[1] that *N,N*-dimethyl-*N*-(2-methyl-1-propylidene)ammonium tetrafluoroborate ("tetramethylketeneimmonium tetrafluoroborate") cycloadds readily to olefins and acyclic dienes to give cyclobutylideneammonium salts in high yield. This new method of building four-membered rings is extremely attractive since: (a) "keteneimmonium ions" do not dimerize or polymerize like ketenes or keteneimines and can thus be stored in solution, and (b) α-chloro enamines, the precursors of "keteneimmonium ions", are easily prepared from inexpensive and readily available starting materials[2]. A severe limitation of the method, however, was the use of the expensive reagent $AgBF_4$ for the generation of the cation from the α-chloro enamine.

We have now developed a simple procedure which does not require $AgBF_4$: addition of *N,N*-dimethyl-1-chloro-2-methylpropenylamine *(1)* to a slurry of freshly dried $ZnCl_2$ in refluxing CH_2Cl_2 gives a salt *(2)* which reacts with olefins to form the cyclobutylideneammonium salts *(3)*. Hydrolysis of the crude salts in 1 N NaOH furnishes the corresponding cyclobutanones *(4)* in high yield (Table 1).

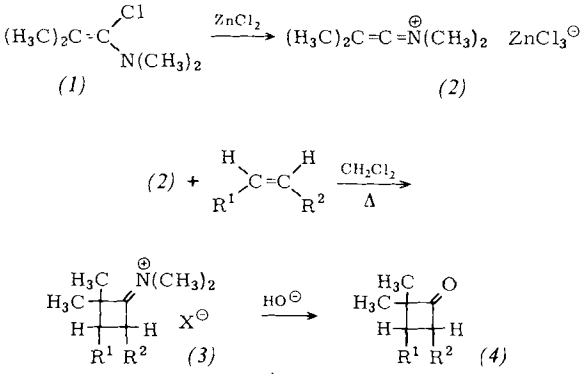


Table 1. Preparation of the salts *(3)* and cyclobutanones *(4)*.

	R^1	R^2	*(3)* [a, b] yield [%]	*(4)* [b] yield [%]
a	H	H	68	89
b		$-(CH_2)_4-$	88	91
c		$-(CH_2)_6-$ [c]	86	97

[a] Isolated as perchlorates.
[b] Identical with authentic samples.
[c] *cis*-Cyclooctene.

It is quite remarkable that *ethylene*, which is normally unreactive in uncatalyzed cycloadditions[3] (for instance, with acrylonitrile it reacts only at 300 °C and 1000 atm.[4]) reacts with *(2)* at room temperature and atmospheric pressure.

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2,2-Dimethylcyclobutanone (4a)

Ethylene (dried by passage through a column filled with $CaSO_4$) is slowly bubbled into a slurry of freshly dried $ZnCl_2$ (2.7 g, 0.02 mol) in CH_2Cl_2 (20 ml). The α-chloro enamine *(1)* (2.25 g, 0.0169 mol) is added from a syringe and the mixture is refluxed for 3 h under a continuous stream of ethylene and then hydrolyzed with 1 N NaOH (40 ml). Extraction with CH_2Cl_2 followed by removal of the solvent yields 1.57 g of *(4a)* still containing 6% of *N,N*-dimethylisobutyramide as shown by vpc.

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[1] *J. Marchand-Brynaert* and *L. Ghosez*, J. Amer. Chem. Soc. *94*, 2870 (1972).

[2] *L. Ghosez, B. Haveaux,* and *H. G. Viehe*, Angew. Chem. *81*, 468 (1969); Angew. Chem. internat. Edit. *8*, 454 (1969); *L. Ghosez*, Angew. Chem. *84*, 901 (1972); Angew. Chem. internat. Edit. *11*, 852 (1972); *L. Ghosez, B. Haveaux, M. Rens, M. Delaunois-Job, M. L. Van der Straten-Ponthoz, E. Sonveaux* and *A. Colens*, unpublished results.

[3] *R. Huisgen, R. Grashey,* and *J. Sauer* in *S. Patai:* The Chemistry of Alkenes. Interscience, New York 1964, p. 739; *R. Huisgen* and *L. Feiler*, Chem. Ber. *102*, 3391 (1969); *P. D. Bartlett, G. M. Cohen, S. P. Elliott, K. Hummel, R. A. Minns, C. M. Sharts,* and *J. Y. Fukunaga*, J. Amer. Chem. Soc. *94*, 2899 (1972); see, however, *L. G. Cannell*, J. Amer. Chem. Soc. *94*, 6867 (1972).

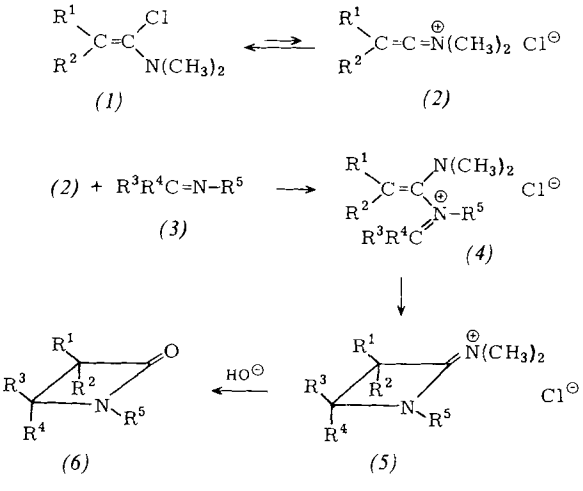
[4] *H. K. Hall, Jr., C. D. Smith,* and *D. E. Plorde*, J. Org. Chem. *38*, 2084 (1973).

A General Method for the Synthesis of 2-Azetidinones and 2-Azetidinylideneammonium Salts[**]

By *Michel De Poortere, Jacqueline Marchand-Brynaert,* and *Léon Ghosez*[*]

The exceptional reactivity of α-chloro enamines *(1)* toward nucleophilic reagents[1] probably results from a fast pre-equilibrium[2] of *(1)* with an alkenylideneammonium chloride *(2)*, which reacts with the nucleophilic reagent.

We have found that the addition of *N,N*-dimethyl-1-chloro-2-methyl-1-propenylamine *(1)*, $R^1 = R^2 = CH_3$, to solutions of



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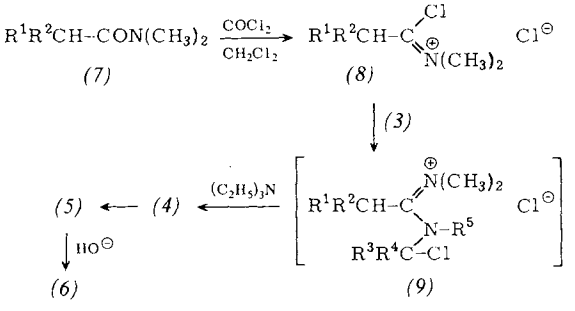
Table 1. Preparation of the salts *(5)* and 2-azetidinones *(6)*.

R^1	R^2	R^3	R^4	R^5	Method	Compound	*(5)* [a] yield [%]	*(6)* [b] yield [%]
CH_3	CH_3	C_6H_5	H	CH_3	A	*a*	74	82
CH_3	CH_3	C_6H_5	H	C_6H_5	A	*b*	47	68
CH_3	CH_3	$C_6H_5CH_2S$	H	$(CH_3)_3C$	A	*c*	60	42
CH_3	CH_3	C_6H_5	C_6H_5	C_6H_5	B	*d*	65	70
H	$(CH_3)_3C$	C_6H_5	H	C_6H_5	B	*e*	80 [c]	0 [d]

[a] As readily crystallizable perchlorates obtained by treatment of the crude chlorides with a saturated solution of $KClO_4$.
[b] Obtained by direct hydrolysis of the crude salts *(5)*. Yields were not optimized.
[c] *trans*-Configuration assigned on the basis of $J_{3,4}=2$ Hz.
[d] Hydrolysis (reflux, 2h) gave the ring-opened product $(CH_3)_3C{-}CH(CON(CH_3)_2){-}CH(C_6H_5){-}NHC_6H_5$ in 76% yield.

the Schiff bases *(3)* in dry CH_2Cl_2 at room temperature (method A) gives the 2-azetidinylideneammonium chlorides *(5)*. Hydrolysis of the crude salts in 0.5 N NaOH affords the corresponding 2-azetidinones *(6)* which show identical properties with authentic samples prepared by known methods (Table 1).

It seems quite probable that the first step in the cycloaddition is aminoalkenylation[1] of the Schiff base *(3)* to give intermediate *(4)* which cyclizes to *(5)*. Since such an intermediate *(4)* is, in principle, also available from the reaction of α-chloro alkylideneammonium chlorides[3] *(8)* with Schiff bases *(3)* followed by elimination of HCl, it appeared feasible to bypass *(1)* and use its direct precursor. Thus crude *(8d)* and *(8e)* obtained from the reaction of tertiary amides *(7d)* and *(7e)* with phosgene[1] were reacted with *(3)* and then treated with triethylamine to give *(5d)* and *(5e)* in good yields (method B). *(5d)* was hydrolyzed readily to the β-lactam *(6d)*. The hydrolysis of *(5e)* on the other hand was much more difficult and resulted in opening of the four-membered ring (see Table 1).



3,3-Dimethyl-1,4,4-triphenyl-2-azetidinone (6d)

Phosgene (7 ml) is added at 0°C to a solution of *N,N*-dimethylisobutyramide *(7a)* (1.15 g, 10 mmol) in dry CH_2Cl_2 (10 ml). After 2 days at room temperature, the solvent is removed *in vacuo* and the residue reacted with a solution of *N*-(diphenylmethylene)aniline (2.56 g, 10 mmol) in CH_2Cl_2 (10 ml). After 3 h, the mixture is treated with triethylamine (1.01 g) and kept at room temperature for 2 h. Filtration to remove the precipitate and evaporation of the solvent *in vacuo* leaves a residue which is hydrolyzed in 0.5 N NaOH (20 ml). The azetidinone is extracted with CH_2Cl_2 (3 × 20 ml), the combined extracts dried ($MgSO_4$), and the solvent evaporated under reduced pressure. Recrystallization from ethanol yields pure *(6d)* (m.p. 122°C).

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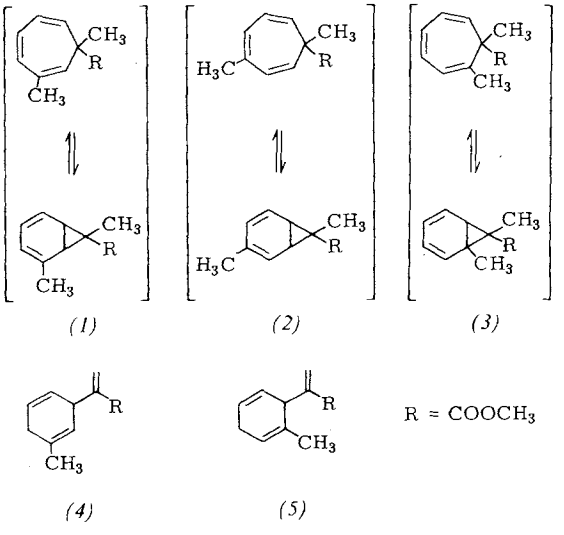
[1] *L. Ghosez, B. Haveaux*, and *H. G. Viehe*, Angew. Chem. *81*, 468 (1969); Angew. Chem. internat. Edit. *8*, 454 (1969); *M. Rens* and *L. Ghosez*, Tetrahedron Lett. *1970*, 3765; *J. Marchand-Brynaert* and *L. Ghosez*, J. Amer. Chem. Soc. *94*, 2869, 2870 (1972).
[2] *M. Rens, A.-M. Frisque-Hesbain*, and *L. Ghosez*, unpublished results.
[3] *H. Eilingsfeld, M. Seefelder*, and *H. Weidinger*, Angew. Chem. *72*, 836 (1960).

Stereochemistry of the Degenerate Norcaradiene Rearrangement: A Stereospecific Symmetry-Forbidden Process[1]

By *Frank-Gerrit Klärner*[*]

The degenerate rearrangement of *cis*-bicyclo[6.1.0]nona-2,4,6-triene follows the course postulated by *Woodward* and *Hoffmann*[2] with a high degree of stereoselectivity. However, it cannot be stated *a priori* whether the stereochemistry is a result of orbital-symmetry control in this system since the least-motion process[3] and orbital symmetry control would both lead to the same result. In contrast, the analogous norcaradiene rearrangement discovered by *Berson* and *Willcott*[4] would proceed with retention at the migrating carbon in an orbital-symmetry controlled reaction[5] but with inversion in the case of a least-motion process. We have studied the stereochemistry of the reaction for optically active methyl 2,7-dimethylnorcaradiene-7-carboxylate *(1)*[6].

Thermolysis of *(1)* (180°C, benzene solution) leads to an equilibrium mixture of the isomers *(1)* to *(5)* [GC: 48.7:39.8:3.1:6.2:2.2] in which *(1)*, *(2)*, and *(3)* are themselves in valence-tautomeric equilibrium with the corresponding cycloheptatriene derivatives[6]. The structures of the new



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compounds are confirmed by their spectroscopic properties; *(3)* was also synthesized by an independent route[6].

The rearrangement of *(1)*, *(2)*, and *(3)* may either be the result of a sigmatropic carbon shift or proceed *via* products *(4)* and *(5)* which are formed by 1,5-homodienyl hydrogen shift. Starting from *(1)*, *(3)*, and *(4)*, the time dependence of the equilibration taken together with the above equilibrium concentrations yielded the rate constants listed in Table 1[7].

Table 1. Rate constants at 180 °C (in benzene).

	(1)→*(2)*	*(1)*→*(3)*	*(1)*→*(4)*	*(2)*→*(4)*	*(2)*→*(1)*	*(3)*→*(1)*	*(4)*→*(1)*	*(4)*→*(2)*
$k \times 10^5$ [s^{-1}]	1.47	2.00	0.61	0.52	1.78	32.09	4.75	3.27

Analysis of these rate constants shows that rearrangement *via (4)* and *(5)* involving a hydrogen shift is only of minor significance ($\leq 10\%$).

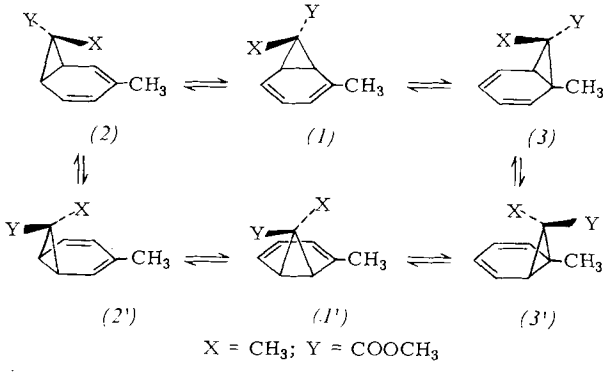
In the case of a sigmatropic carbon shift *(2)*⇌*(1)*⇌*(3)* with *retention*, loss of optical purity of the reactants on equilibration must correspond to the degree of participation of the homodienyl hydrogen shift in the isomerization[8]. If the rearrangement steps proceed with *inversion*, however, then racemization can only occur in the reactions *(2)*⇌*(2')* and *(3)*⇌*(3')*.

Table 2. Racemization of optically active *(1)*.

t [s]	c [a] (exp.)	c [a] (calc.) [b]
0.6288×10^5	80.7	81.1
1.3454×10^5	47.5	46.7
2.3406×10^5	22.8	21.1

[a] c [%] = 100 × [α]/[α]$_0$; [α]$_0$ = rotation of the starting compound, [α] = rotation of *(1)* isolated by gas chromatography.
[b] Calculated values for inversion at C^7 with $k_{22'} = 1.5$ and $k_{33'} = 0.9 \times 10^{-5}$ [s^{-1}].

As seen from Table 2, the rate of racemization of *(1)* could be simulated by an analog computer[9] utilizing the rate constants given in Table 1.



X = CH_3; Y = $COOCH_3$

The reaction scheme could be tested by thermolysis of both optically active *(1)* and optically active *(2)*. Rearrangement products *(2)* and *(3)* obtained on thermolysis of *(1)*, as well as recovered *(1)*, were found to be optically active, as expected. Their optical purity (O.P.), determined with chiral NMR shift reagents[10], agreed with the calculated values within the limits of accuracy of the method (Table 3) when the rate constants from Table 1 were again used in the calculations. The optical purity of *(3)* demonstrates that the stereoselectivity of the migration of C^7 is certainly in excess of 97.5% and according to calculation should be almost 100%.

Table 3. Thermolysis of *(1)* ($[\alpha]_{436}^{25} = +333.8$; O.P.$_0$ = 52.8%).

Product spread [%]	$[\alpha]_{436}^{25}$ [°]	O.P. [%]	c [a] (exp.)	c [a] (calc.)
(1): 65.6	+325.7	51.8	98	93
(2): 27.7	+ 12.5	27.2	52	59
(3): 6.7	+ 59.8	50.2	95	89

[a] c [%] = 100 × O.P./O.P.$_0$.

In contrast, thermolysis of optically active *(2)* (O.P. 27.2%) leads to extensive racemization of the reactant (O.P. 8%) after formation of only 25% of *(1)* and to a high optical purity of the rearrangement product *(1)* (O.P. 18%). This finding rules out a carbon shift with retention. Under the experimental conditions such a process would result in almost complete retention of the optical purity of *(2)* (98%), which cannot be reconciled with the considerable loss (29%) actually observed.

The degenerate rearrangement of norcaradiene[11] and likewise that of *cis*-bicyclo[6.1.0]nona-2,4,6-triene thus proceed with inversion at the migrating carbon, regardless of the fact that in norcaradiene an antiaromatic transition state is formally involved[12]. In the transition state the distance between the interacting orbitals on C^1, C^7, and C^5 is apparently so great that significant overlap is no longer possible and no perceptible electronic stabilization or destabilization occurs.

An explanation[13] for the observed stereochemistry is provided by a least-motion process. Unlike the geometrical isomerization of cyclopropane, the degenerate rearrangement of norcaradiene or *cis*-bicyclo[6.1.0]nona-2,4,6-triene merely requires excitation of a C—C stretching vibration. Once the parting C atoms (C^1—C^7) have left the region of bonding interaction, C^7 will continue its motion until it is "captured" by interaction with C^5, which necessarily leads to inversion. In cyclopropane itself[14] such a process is impossible since the forces retaining the configuration at C^3 will very soon come into play following rupture of the C—C bond to prevent further widening of the angle C^{1}C^{2}C^3 and thus effect restoration of the original bond.

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[1] This work was supported by the Deutsche Forschungsgemeinschaft.

[2] *F.-G. Klärner*, Angew. Chem. *84*, 892 (1972); Angew. Chem. internat. Edit. *11*, 832 (1972).

[3] *J. Hine*, J. Org. Chem. *31*, 1236 (1966); and further literature cited therein.

[4] *J. A. Berson*, Accounts Chem. Res. *1*, 152 (1968); and further literature cited therein.

[5] *R. B. Woodward* and *R. Hoffmann*, Angew. Chem. *81*, 797 (1969); Angew. Chem. internat. Edit. *8*, 781 (1969).

[6] The synthesis of *(1)* and *(3)* and the norcaradiene-cycloheptatriene equilibria will be reported elsewhere.

[7] At 180 °C (benzene solution) $k_{51} + k_{53} \approx k_{41} + k_{42}$.

[8] Methyl α-(4-methyl-2,5-cyclohexadienyl)acrylate and methyl α-(1-methyl-2,5-cyclohexadienyl)acrylate could not be detected among the rearrangement products, and making the reasonable assumption that the rate constant of the homodienyl hydrogen shift of these products is comparable with those of *(4)* and *(5)* we can exclude any racemization involving them.

[9] The author is grateful to Professor Dr. *G. Bergmann* and Ing. *R. Baese* for assistance in the use of an analog computer.

[10] Tris[3-(heptafluoro-1-hydroxybutylidene)-(+)-camphorato]europium-(III), Willow Brook Laboratories, Inc.; *H. L. Goering, J. N. Eikenberry,* and *G. S. Koermer,* J. Amer. Chem. Soc. *93,* 5913 (1971).

[11] Preliminary experiments show that the degenerate rearrangement of 2,7-dimethylnorcaradiene-7-carbonitrile also proceeds with inversion.

[12] *M. J. S. Dewar,* Tetrahedron Suppl. *8,* 75 (1966); Angew. Chem. *83,* 859 (1971); Angew. Chem. internat. Edit. *10,* 761 (1971).

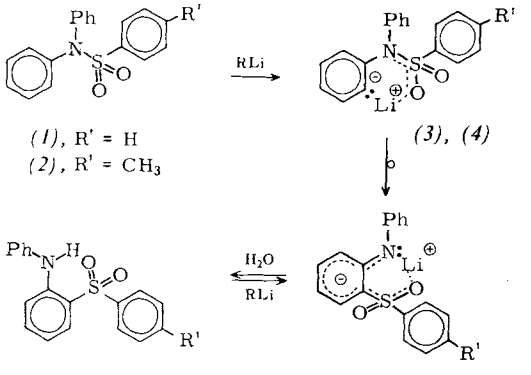
[13] For alternative explanations, see: *J. A. Berson* and *L. Salem,* J. Amer. Chem. Soc. *94,* 8917 (1972); *W. Schoeller,* unpublished.

[14] *W. v. E. Doering,* Lecture delivered on September 4, 1972, Universität Bochum.

The Sulfonamide-Aminosulfone Rearrangement: A Rearrangement Induced Anionically, Cationically, and Thermally[**]

By *Dieter Hellwinkel* and *Martin Supp*[*]

During attempts to synthesize triarylamines utilizing organolithium compounds, we treated *N,N*-diphenylbenzenesulfonamide *(1)* and the corresponding *p*-toluenesulfonamide *(2)* with phenyl-, butyl- and methyl-lithium. However, we did not obtain the desired products of a nucleophilic substitution of the benzenesulfinate groups, but instead the isomers *(7)* and *(8)* of the starting compounds (showing intense NH stretching vibrations at 3348 cm^{-1}). We also isolated varying amounts of diphenylamine as a by-product. The constitution of *(7)* as a 2-anilinodiphenyl sulfone was proved by comparison with the reaction product of 1,2-bis(phenylsulfonyl)benzene with potassium anilide[1]. Hence *(8)* is the 2-anilino-4'-methyldiphenyl sulfone. We interpret the reaction as proceeding *via* the following sequence:



(1), R' = H
(2), R' = CH_3

(3), *(4)*

(7), m.p. 77 °C
(8), m.p. 94 °C

(5), *(6)*

Table 1. Reaction of sulfonamides *(1)* and *(2)* with organolithium reagents RLi.

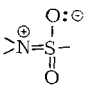
Substrate	RLi, R=	Solvent	T [°]	t [h]	Yield [%] (7)	(8)	$(C_6H_5)_2NH$
(1)	C_6H_5	[a]	0	5	57		6
	C_6H_5	[b]	0	2	61		3
	n-C_4H_9	[a]	0	5	58		3
	n-C_4H_9	[b]	0	2	55		3
	CH_3	[a]	0	5	26		4
(2)	C_6H_5	[a]	34	3		48	25
	n-C_4H_9	[a]	34	3		43	—
	n-C_4H_9	[b]	60	3		37	11

[a] Diethyl ether.
[b] Tetrahydrofuran.

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Remarkably, the phenyl ring bound to the nitrogen is clearly the one which is metalated. This suggests an important resonance contribution of the type



to the ground state of these sulfonamides whose positively charged nitrogen will now favor metalation[2]. The driving force for the rearrangement, which takes place under surprisingly mild conditions, can be seen in the transformation of the phenyl anions *(3)* and *(4)* into the resonance-stabilized nitrogen anions *(5)* and *(6)* respectively. The considerable reaction rate follows from the immediate yellow (in ether) or orange coloration (in THF) due to the anions *(5)* and *(6)* upon addition of RLi to the sulfonamides.

It has long been known that the same products *(7)* and *(8)* are formed in the reaction of *(1)* and *(2)* with concentrated sulfuric acid[3]: we have now also confirmed this reaction (yield > 50%). The MO models which can be formulated for a cationic rearrangement transition state, making the plausible assumption of an intramolecular[4] synchronous reaction, are equally valid for a purely thermal process. Indeed, thermolysis of the sulfonamide *(1)* at 230°C (12 h) gave up to 26% of sulfone *(7)*.

We consider that a similar trichotomy of rearrangement possibilities likewise may well hold for (di)phenylamine derivatives substituted by other acid moieties.

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[1] *G. Köbrich,* Chem. Ber. *92,* 2981 (1959). We thank Prof. *Köbrich* for a reference sample.

[2] Preferred metalation of the phenyl ring directly bound to the sulfonyl group could have been expected since diphenyl sulfone is known to be metalated very easily in the *ortho* position by butyl lithium [cf. *J. M. Mallan* and *R. L. Bebb,* Chem. Rev. *69,* 693 (1969)]. Therefore, a kinetically controlled primary metalation of the corresponding positions in *(1)* and *(2)* and subsequent transmetalation cannot be excluded. It has meanwhile (*note added in proof.* March 8, 1974) been proved.

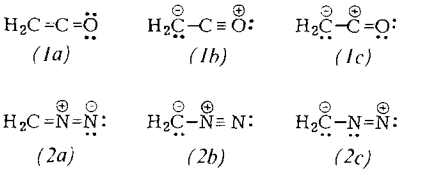
[3] *J. Halberkann,* Ber. Deut. Chem. Ges. *55,* 3074 (1922).

[4] Cf. *M. J. S. Dewar* in *P. de Mayo:* Molecular rearrangements. Wiley-Interscience, New York 1963, Vol. 1, p. 308.

^{13}C-NMR Spectra of Diazoalkanes[1]

By *Joachim Firl, Wolfgang Runge,* and *Werner Hartmann*[*]

From the extreme shielding of the terminal C atom and the resonance position of the central C atom in the ^{13}C-NMR spectrum of ketene *(1)*[2] we have concluded, in agreement with other experimental results, that the resonance structure *(1b)* contributes essentially to the ground state. The corresponding resonance structure *(2b)* is generally accepted to be the most important form in the VB description of the isoelectronic diazomethane *(2)*[3,4].



(1a) *(1b)* *(1c)*

(2a) *(2b)* *(2c)*

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Table 1. ^{13}C-NMR data for diazoalkanes $R^1R^2C{=}N_2$, $\delta_{C(TMS)}$ [ppm] [a].

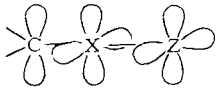
Compound	R^1	R^2	$\delta_{C(CN_2)}$	$\delta_{C(R^2)}$	δ_{C_p}
(2)	H	H	23.1	—	—
(3)	C_6H_5	H	47.2	—	123.8
(4)	C_6H_5	CH_3	51.2	10.0 (CH_3)	123.4
(5)	C_6H_5	C_2H_5	57.2	16.9 (CH_3), 11.1 (CH_2)	123.2
(6)	C_6H_5	C_6H_5	62.5	129.3 (C_o), 129.0 (C_m), 124.9 (C_p)	125.4
(7)	H	CO_2CH_3	46.3	167.6 (CO), 52.1 (OCH_3)	—

[a] From broad-band decoupled PFT spectra in $CDCl_3$ at 0°C with TMS as internal standard; Bruker HX 90 NMR spectrometer; 22.63 MHz.

Since C atoms in similar bonding situations show analogous NMR shifts, a shielding comparable to that in ketene can be expected for the (terminal) C atom in diazomethane. To substantiate this, we have recorded the ^{13}C-NMR spectra of a series of diazoalkanes (see Table 1).

The characteristic feature of these spectra is the extreme shielding of the formally sp^2-hybridized diazomethylene carbon [typical signal range from 23.1 (diazomethane) to 62.5 ppm (diphenyldiazomethane)]. Its resonance position differs considerably from that hitherto regarded as normal for sp^2-hybridized carbon doubly bonded to nitrogen. In comparison with analogously substituted imines, the resonance of this C atom is shifted 100—120 ppm upfield. The shielding of the sp^2 C in diazoalkanes is exceeded only by that of the terminal C atom in the isoelectronic ketenes[1,5].

The theory of chemical shifts predicts increasing shielding for increasing electron density. The anomalous shielding of the sp^2 C atom found for both ketenes and diazoalkanes qualitatively confirms the close similarity of the π bonding in the two classes of compounds (high π-electron density on sp^2 C). The paramagnetic shift of the methylene C atom in diazoalkanes relative to the ketenes is presumably attributable solely to the greater electronegativity of the N_2 group compared to that of the CO group and the resulting reduction in the σ-electron density.



The π-electronic structure of ketene and diazomethane can be described by two orthogonal π systems[4], of which one (occupied by two electrons) is delocalized over two centers (CO, NN) and the other over three centers, from the terminal hetero atom to the terminal C atom. The second system contains four electrons and is thus isoelectronic to the allyl anion. The anomalous shielding of the terminal C atoms seems to be connected with this special electronic and nuclear configuration. Such a conclusion is supported by similarly exceptional ^{13}C-NMR data for classes of compounds having similar bonding, for instance the nitrile oxides recently described by *Roberts et al.*[6].

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[1] Part of a lecture delivered at the Fall Meeting of the Deutscher Arbeitskreis für Spektroskopie, Düsseldorf, October 1973. This work was supported by the Deutsche Forschungsgemeinschaft.

[2] *J. Firl* and *W. Runge*, Angew. Chem. 85, 671 (1973); Angew. Chem. internat. Edit. 12, 668 (1973).

[3] *C. B. Moore* and *G. C. Pimentel*, J. Chem. Phys. 40, 1529 (1964).

[4] *J. Del Bene* and *H. H. Jaffé*, J. Chem. Phys. 50, 1126 (1969).

[5] *G. A. Olah* and *P. W. Westermann*, J. Amer. Chem. Soc. 95, 3766 (1973).

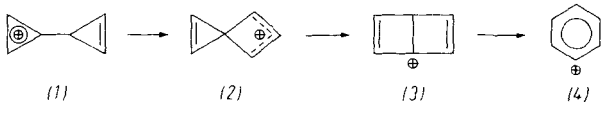
[6] *M. Christl, J. P. Warren, B. L. Hawkins*, and *J. D. Roberts*, J. Amer. Chem. Soc. 95, 4392 (1973).

Synthesis and Trapping Reactions of the Spiro[2.3]-hexadienylium System: Ring strain *versus* Aromaticity[1]

By *Robert Weiss* and *Steffen Andrae*[*]

Calculation of the enthalpy gradient between bicyclopropenyl and benzene using standard bond increments and the experimentally determined cyclopropene ring strain[2] yields a value of about 124 kcal. We are attempting a systematic exploitation of the synthetic potential implied by this value in conversions in the $(CH)_6$ series[3,4].

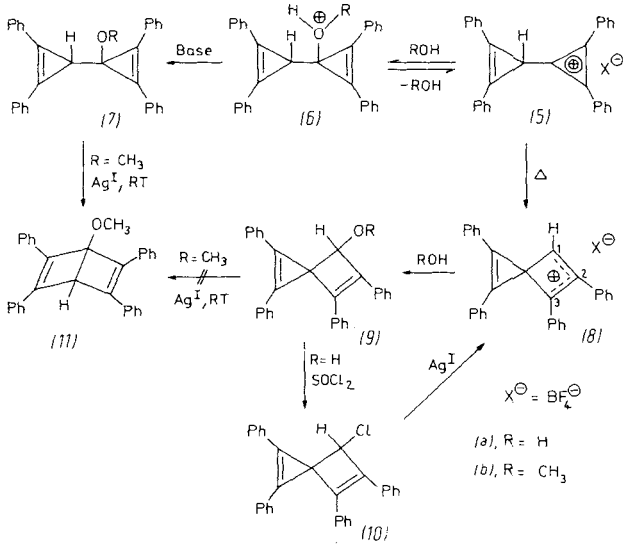
We have now studied the question whether the "ring-strain controlled" rearrangement of bicyclopropenyl to benzene derivatives has a counterpart in the $C_6H_5^{\oplus}$ series. An estimate of the relative enthalpies of the cyclopropenylcyclopropenylium cation *(1)* and the phenyl cation *(4)* reveals that the energy content of *(1)* is some 113 kcal greater than that of (singlet) *(4)*. The *thermodynamic conditions* for a conversion *(1)*→*(4)* are therefore favorable. An intervention of the intermediates *(2)* and *(3)* would also satisfy the *topological conditions* for such a transition.



(1) *(2)* *(3)* *(4)*

In the present communication we report the first step of this sequence: the rearrangement of a cyclopropenylcyclopropenylium ion to the hitherto unknown spiro[2.3]hexa-1,4-dienylium system and its trapping reactions (see reaction scheme).

As starting compound we chose the readily accessible cyclopropenylium ion *(5)*[5] which can also be regarded as an ideally



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stabilized cyclopropenylmethyl cation. This particular structural feature finds expression in a dualistic behavior. Thus *(5)*, for example, reacts with ROH (R = H, CH_3) at room temperature on addition of base to give bicyclopropenyl systems *(7)*[6] (when R = H the characteristic cyclopropenol ring opening ensues[7]).

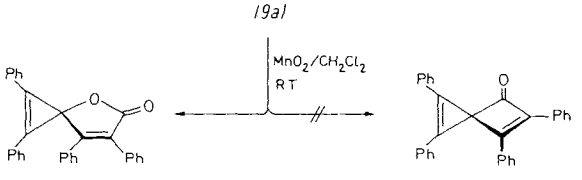
In the absence of an auxiliary base, however, a mobile equilibrium *(5)* $\rightleftharpoons$ *(6)* can be set up. At only slightly elevated temperatures (boiling CH_2Cl_2) the ring expansion *(5)*→*(8)* takes place within a few hours. Compared with *(5)*, *(8)* is the hotter carbonium ion and can be trapped irreversibly by water or methanol to give spiro[2.3]hexadienes *(9)*; predictably, the nucleophile attacks *(8)* exclusively at position 1. The first example of the theoretically interesting[8] class of compounds *(9)* was recently prepared by total synthesis[9]. Our preparation is simpler, gives higher yields, and is in principle more versatile (by using different trapping reagents[10]). The structures of the spirobicyclics *(9)* are confirmed by their analytical and spectroscopic data (Table 1) and by chemical evidence.

Table 1. Yields and physical properties of spiro[2.3]hexadienes *(9)*.

Cpd.	Yield [%]	M.p. [°C]	IR (KBr) [cm⁻¹]	NMR ($CDCl_3$) τ	MS *m/e*
(9a)	51	138	1802 [a]	8.03 (1H, s, br), OH [b] 4.65 (1H, s)	398 ($M^{\oplus}$) base peak
(9b)	68	124	1800 [a]	6.65 [3H, s) 4.88 (1H, s)	412 ($M^{\oplus}$) base peak

[a] C C (cyclopropene).
[b] Signal disappears on shaking with D_2O.

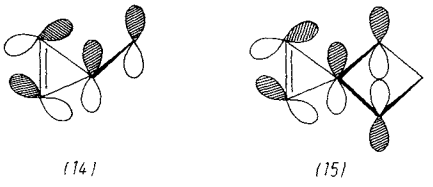
On treatment with $SOCl_2/K_2CO_3$ in anhydrous CH_2Cl_2 at room temperature *(9a)* is converted into *(10)* [colorless oil; characteristic methine proton at τ = 4.40 (1H)]. *(10)* is suitable as neutral source of the spiro[2.3]hexadienylium system *(8)* on action of $Ag^{\oplus}$ ions: in CH_3OH *(9b)* is formed in this way. Oxidation of *(9a)* with MnO_2 provides a structural bridge to a known substance: the product is not the highly strained spiroketone *(12)*, but instead the dimer of diphenylcyclopropenone *(13)*.



Together with the data listed in Table 1 this reaction amounts to structural proof for *(9a)*.

Neither the reverse reaction *(8)*→*(5)* nor reactions ensuing therefrom could be observed. Although *(8)* would appear to be geometrically predestinated for rearrangement to the corresponding Dewar benzene cation, on account of the bisected arrangement of the cyclopropene σ bond and the allyl cation moiety[11], no such reaction occurs [corresponding to *(2)*→*(3)*] under the reaction conditions employed. The possibility that $Ag^{\oplus}$ catalyzed rearrangement[4] of *(7b)* to *(11)* might proceed *via* *(9b)* could be discounted: *(9b)* is inert towards $Ag^{\oplus}$ under conditions of rearrangement[4]. Viewed together, our experimental findings strongly suggest that the spiro[2.3]hexadienylium system represents a pronounced local minimum on the $C_6H_5^{\oplus}$ potential energy surface.

What provides the driving force for the unusual ring expansion *(5)*→*(8)*? An estimate[12] of the enthalpy changes involved in the rearrangement *(1)*→*(2)* shows that about 80—90% of the resonance energy of *(1)* is already provided by the drop in total strain energy; together with the resonance energy of the resulting cyclobutenyl cation it is even overcompensated by at least 7 kcal/mol. The energetics of *(5)*→*(8)* should be essentially similar. However, whereas the anionic counterpart of *(2)* can be stabilized by spiroconjugation[8] and the bisected cyclopropenylmethyl cation *(14)*[11] by σ-π interaction, these two possibilities are ruled out for *(2)* for symmetry reasons[8] (cf. *(15)*[15]).



(14) *(15)*

Any perturbation producing asymmetry in the allyl LUMO, however, causes admixture of the highest occupied cyclopropene Walsh orbital to this orbital and thereby effects a stabilization of the spirocation. Owing to the reduced symmetry of the system, this should also apply to *(8)*. No statement is yet possible about the magnitude of this effect.

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[1] Reactions of Coupled Three-Membered Rings, Part 5. This work was supported by the Deutsche Forschungsgemeinschaft.—Part 4: *R. Weiss, C. Schlierf*, and *H. Kölbl*, Tetrahedron Lett. *1973*, 4827.

[2] *M. J. S. Dewar*: The Molecular Orbital Theory of Organic Chemistry. McGraw-Hill, New York 1970, p. 461.

[3] *R. Weiss* and *C. Schlierf*, Angew. Chem. *83*, 887 (1971); Angew. Chem. internat. Edit. *10*, 811 (1971).

[4] *R. Weiss* and *St. Andrae*, Angew. Chem. *85*, 145, 147 (1973); Angew. Chem. internat. Edit. *12*, 150, 152 (1973).

[5] *R. Breslow, P. Gal, H. W. Chang*, and *L. J. Altmann*, J. Amer. Chem. Soc. *87*, 5139 (1965). To our knowledge, *(5)* is the only stable derivative of a $C_nH_5^{\oplus}$ system so far reported.

[6] The corresponding isomeric 1,3'-bicyclopropenyls are formed as well, cf. ref. [4].

[7] *Houben-Weyl*: Methoden der Organischen Chemie. Thieme, Stuttgart 1971, Vol. 4/3, p. 774.

[8] *H. E. Simmons* and *T. Fukunaga*, J. Amer. Chem. Soc. *89*, 5208 (1967); *R. Hoffmann, A. Imamura*, and *G. D. Zeiss*, *ibid.* *89*, 5219 (1967).

[9] *M. F. Semmelhack* and *R. J. DeFranco*, J. Amer. Chem. Soc. *94*, 8838 (1972).

[10] According to preliminary experiments, *(8)* is also scavenged as spiro[2.3]hexadienes *e.g.* by Friedel-Crafts reaction with aromatic compounds.

[11] Cf. *R. Breslow, J. Lockhart*, and *A. Small*, J. Amer. Chem. Soc. *84*, 2793 (1962).

[12] This estimate is based on the following values:
1) strain energies: a) cyclopropene 54 [2], b) cyclopropenylium ion 74 (= 20 + 54 [13]), c) spiro[2.3]hexadiene 85 kcal/mol [9]; the *upper limit* for the corresponding *cation (2)* was assumed to be 10 kcal/mol higher, on account of the additional angular strain.—2) Resonance energies: a) cyclopropenylium ion *ca.* 39 kcal/mol [13]; an additional drop in energy of the cyclopropenylium ion owing to the donor effect of a cyclopropene substituent as in *(1)* was accounted for by a value of 7 kcal/mol (upper limit) in the calculation [14]. b) cyclobutenyl cation: the resonance energy of the allyl cation (≥ 20 kcal/mol [13]) was adopted as a *lower limit*.

[13] *R. Breslow* in *M. Oki*: Nonbenzoid Aromatic Compounds. Sendai 1970, pp. 111—130.

[14] This value is deduced from pK_{R^+} measurements on *(5)*; *R. Weiss* and *C. Schlierf*, unpublished.

[15] The orbitals schematically depicted in *(15)* are the highest occupied σ orbital ("Walsh orbital") of cyclopropene and the lowest unoccupied π orbital of the cyclobutenyl portion of *(2)*.

A Method for the Evaluation of Inductive and Conjugative Effects—Application to Tropone[1]

By *Claus Müller, Armin Schweig,* and *Hans Vermeer*[*]

In this contribution we wish to point out a powerful method[2-4] *for evaluating inductive and conjugative effects and for distinguishing one from the other.* The quantitative rationalization of such effects is of fundamental importance in organic chemistry.

The method will be illustrated for the case of tropone *(2)*. For this purpose, we start from the measured[5-7] orbital energies of the two highest occupied π MOs of 1,3,5-cycloheptatriene *(1)*. In model calculations we then account, step by step, for all conformational, conjugative, and inductive energy changes suffered by both MOs when going from nonplanar[8] *(1)* to planar[9] *(2)*. Finally we compare the predicted orbital energies of the two highest occupied π MOs of *(2)* with those measured by photoelectron (PE) spectroscopy[6,7]. Good agreement between predicted and measured values then confirms the reliability of the derived conjugative and inductive effects.

The transformation of the two highest occupied π MOs of *(1)* to the corresponding $\pi(b_1)$ (no node at the carbonyl group) and $\pi(a_2)$ (node at the carbonyl group) MOs in *(2)* involves four steps (cf. Fig. 1): 1) Evaluation of the conformational effect. These effects are the MO energy changes occurring on transformation of *(1)* to planar cycloheptatriene *(1a)*. The conformational effect reflects the change of all π-π and σ-π (hyperconjugative) interactions in the transition of *(1)*

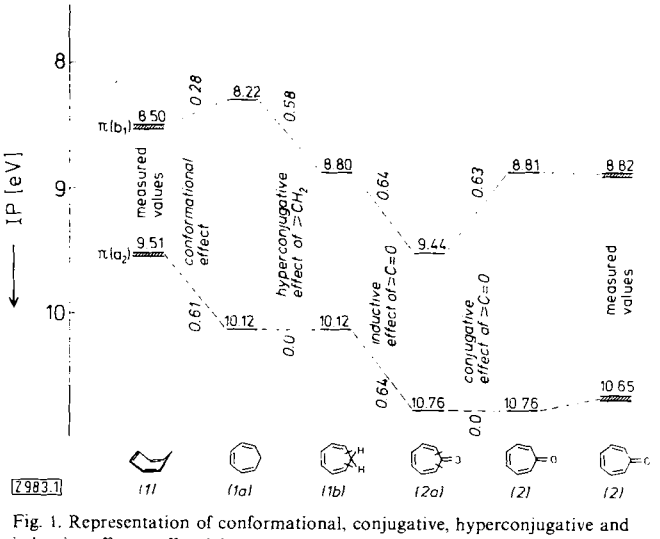


Fig. 1. Representation of conformational, conjugative, hyperconjugative and inductive effects suffered by the two highest occupied π MOs when going from 1,3,5-cycloheptatriene *(1)* to tropone *(2)*. The dashes across the C—C bonds in *(1b)* and *(2a)* symbolize the conjugative decoupling applied to these systems.

to *(1a)*.—2) Calculation of the hyperconjugative effect of the CH_2 group in *(1a)*. Accounting for this effect we arrive at π MO energies of fictitious cycloheptatriene *(1b)* that are not influenced by hyperconjugation.—3) Evaluation of the inductive effect of the carbonyl group. Taking account of this effect we obtain π MO energies of fictitious cycloheptatrienone *(2a)* which are influenced by the inductive effect of the carbonyl group but are free from conjugative effects.—4) Calculation of the remaining conjugative effect of the carbonyl group. Thus we finally arrive at the theoretically predictable $\pi(b_1)$ and $\pi(a_2)$ MO energies of *(2)*.

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The calculation of all the effects listed in 1) to 4) is based on the MINDO/2 method. The conformational effect is evaluated from the difference between corresponding MO energies of *(1a)* and *(1)*. The hyperconjugative effect exerted by the CH_2 group in *(1a)* results from the difference between the corresponding MO energies of *(1a)* and *(1b)*. The calculation of *(1b)* is carried out with conjugative decoupling of the CH_2 group[2-4]. The conjugative effect of the carbonyl group is computed in an analogous manner[2-4] by comparing *(2)* and *(2a)*. Finally the inductive effect of the carbonyl group follows from the energy difference between corresponding MOs in *(2a)* and *(1b)*.

Most impressively, the MO energies of *(2)* predicted in the above manner are in excellent agreement with the measured values. Thus the observed stabilization of the $\pi(b_1)$ and $\pi(a_2)$ MOs (0.32 and 1.14 eV, respectively) are reproduced very satisfactorily by the theoretical values (0.31 and 1.24 eV). On the basis of these results there is good reason to assume that the individual computational steps are reliable too. In particular, the following results warrant attention: 1) Due to the conformational effect the $\pi(a_2)$ MO is stabilized to twice the extent that the $\pi(b_1)$ MO is destabilized; 2) *the hyperconjugative effect of the CH_2 group and the conjugative effect of carbonyl group on the $\pi(b_1)$ MO are nearly the same*; 3) *the inductive effect of a carbonyl group on both π MOs has the same value*; 4) the inductive and conjugative effects of the carbonyl group on the $\pi(b_1)$ MO are expectedly opposite in sign, but of the same magnitude; and last but not least 5) *the conjugative effect between the carbonyl group and the $\pi(b_1)$ MO in (1b) is appreciable (0.63 eV).*

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[1] Part 43 of "Theory and Application of Photoelectron Spectroscopy". This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 42: *H. Schmidt, A. Schweig, A. G. Anastassiou,* and *H. Yamamoto,* J. C. S. Chem. Comm., in press.

[2] *N. C. Baird,* Theor. Chim. Acta *16*, 239 (1970).

[3] *H. L. Hase* and *A. Schweig,* Tetrahedron *29*, 1759 (1973).

[4] The method was introduced by *Baird* [2] to obtain hyperconjugation energies for alkyl-substituted unsaturated compounds. We have now extended it and applied it for the first time to conjugative decoupling of two arbitrarily chosen π units in a larger π system.

[5] *C. Batich, P. Bischof,* and *E. Heilbronner,* J. Electron Spectrosc. *1*, 333 (1972/73). The values used in this contribution (Fig. 1) are based on our own measurements.

[6] *C. Müller* and *A. Schweig.* The PE spectrum of *(2)* exhibits three bands prior to the onset of σ ionization: ①/8.82 eV/π (b_1); ② 9.17 eV/n (oxygen atom); ③/10.65 eV/π (a_2). The bands were assigned by comparison with the spectra of *(1)* and of cycloheptanone [9.07 eV/n (oxygen atom)] in conjugtion with quantum chemical calculation. The PE spectrum of *(2)* has also been measured and interpreted by *J. C. Bünzli, D. C. Frost,* and *L. Weiler,* personal communication. The two interpretations are in mutual agreement.

[7] Assuming the validity of Koopmans' theorem: *T. Koopmans,* Physica *1*, 104 (1934).

[8] *S. Buttcher,* J. Chem. Phys. *42*, 1883 (1965).

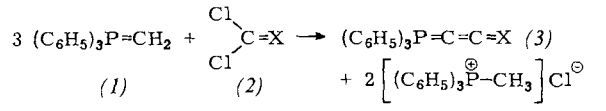
[9] *M. J. Barrow, O. S. Mills,* and *G. Filippini,* J. C. S. Chem. Comm. *1973*, 66.

A New Synthesis of Keteniminylidenetriphenylphosphoranes and Thioketenylidenetriphenylphosphorane

By *Hans Jürgen Bestmann* and *Günter Schmid*[*]

On reaction of methylenetriphenylphosphorane *(1)* with isocyanide dichlorides *((2)*, X=N—R) in a molar ratio of 3:1 double transylidation[1] occurs to give keteniminylidenetriphenylphosphoranes *((3)*, X=N—R) alongside methyltri-

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phenylphosphonium chloride which precipitates from the reaction solution.

The analogous reaction of compound *(1)* with thiophosgene (*(2)*, X = S) furnishes thioketenylidenetriphenylphosphorane (*(3)*, X = S)[2].

Table 1. Products of type *(3)*.

Compound	X	M.p. [°C]	Yield [%]
(3a)	N—C_6H_5	151—152	80
(3b)	N—*p*-C_6H_4Cl	183	75
(3c)	N—*o,p*-$C_6H_3Cl_2$	161	73
(3d)	N—CH_3	157—158	70
(3e)	N—C_6H_{11}	137—139	68
(3f)	S	218—220	60

The IR spectra of compounds *(3)* all contain a strong cumulene band at 2000 cm^{-1}; an additional absorption at 2150 cm^{-1} is observed in the case of *(3f)*.

Experimental:

An isocyanide dichloride (150 mmol) is added dropwise to a stirred salt-free solution[1b] of methylenetriphenylphosphorane (124 g, 450 mmol) in benzene/tetrahydrofuran (1:1, 1 l). After 1 h the precipitate (methyltriphenylphosphonium chloride), is filtered off under suction, the solvent distilled off from the filtrate, and the residue recrystallized from ethyl acetate. The yields and melting points of the resulting keteniminylidenetriphenylphosphoranes are listed in Table 1.

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[1] a) *H. J. Bestmann*, Chem. Ber. 95, 58 (1962); b) Angew. Chem. 77, 609 (1965); Angew. Chem. internat. Edit. 4, 583 (1965).

[2] For a completely different synthesis of compounds *(3)*, see: *C. N. Matthews* and *G. H. Birum*, Tetrahedron Lett. *1966*, 5707; J. Amer. Chem. Soc. 90, 3842 (1968); *G. H. Birum* and *C. N. Matthews*, Chem. Ind. (London) *1968*, 653.

Synthesis and Reactions of Unstabilized α-Selenonio Alkylides

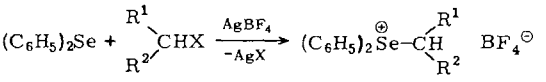
By *Willy Dumont*, *Pierre Bayet*, and *Alain Krief*[*]

Highly stabilized and unreactive α-selenonio alkylides have been described in the literature[1-4]; however, little[5] is known about the reactivity of the unstabilized derivatives towards electrophilic compounds. We therefore investigated whether unstabilized selenonium salts *(1)* can undergo nucleophilic reaction as carbene precursors or potential carbenoids or ylides in presence of a base.

For our study we required selenonium salts having three identical substituents on the selenium, *e.g.* trimethylselenonium iodide *(1a)*[6]

$(CH_3)_3Se^{\oplus}I^{\ominus}$ *(1a)*

or having two substituents bearing no α-hydrogen, *e.g.* alkyldiphenylselenonium salts *(1b)*—*(1d)*. We have now prepared these last salts, which were hitherto unknown, by treating diphenyl selenide[7,8] with an excess of alkyl iodide (or bromide) in the presence of a stoichiometric amount of silver tetrafluoroborate (see *Experimental* and Table 1).



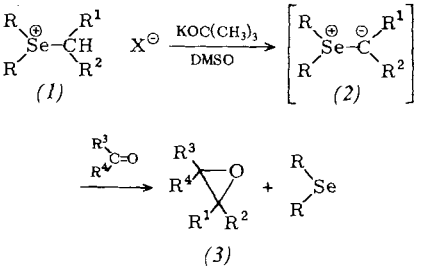
(1b) - *(1d)*

Table 1. Synthesized alkyldiphenylselenonium tetrafluoroborates *(1b)*—*(1d)*.

(1)	R^1	R^2	X	Yield [%]	M.p. [°C]
b	H	H	I	60	92 [a]
c	H	CH_3	Br	50	oil at 20°C
d	CH_3	CH_3	I	36	111 [a]

[a] From ethanol.

The salts *(1a)*, *(1b)*, and *(1c)* were reacted with strong bases to yield the corresponding selenonio alkylides (carbanions) *(2a)*, *(2b)*, and *(2c)*. We discovered that carbanions *(2)* generated *in situ* by use of potassium *tert*-butoxide react with nonenolizable aldehydes or ketones to form the corresponding oxiranes (epoxides) (Table 2)[9].



(1) *(2)* *(3)*

Table 2. Oxiranes *(3)* [a] prepared from selenonium salts *(1)* *via* selenonio alkylides *(2)*. The quoted yields apply to the purified oxiranes.

	R	R^1	R^2	R^3	R^4	*(3)*, yield [%]
(1a)	CH_3	H	H	C_6H_5	H	90
(1a)	CH_3	H	H	*p*-CH_3—OC_6H_4	H	75
(1a)	CH_3	H	H	*p*-NC—C_6H_4	H	54
(1a)	CH_3	H	H	mesityl	H	79
(1a)	CH_3	H	H	C_6H_5CH=CH	H	71
(1a)	CH_3	H	H	C_6H_5CH=CH	C_6H_5	50
(1b)	C_6H_5	H	H	C_6H_5	H	90
(1a)	CH_3	H	H	C_6H_5	C_6H_5	90
(1c)	C_6H_5	H	CH_3	C_6H_5	H	69

[a] IR and NMR spectra were in accord with the structures given for compound *(3)*.

In addition, dimethylselenonio methylide *(2a)* reacted with cinnamaldehyde and chalcone[10] to give the corresponding oxiranes in 71% and 50% yield, respectively, free from any cyclopropane derivative.

When subjected to the same procedure, enolizable carbonyl compounds such as heptanal, cyclohexanone, methyl ethyl ketone, and acetophenone, did not form significant amounts of the corresponding oxiranes. In the reaction of acetophenone with selenonium salt *(1a)* or *(1b)*, we observed an alkylation leading to propiophenone (13%) and isobutyrophenone (28%); 40% of unreacted acetophenone were also isolated. To account for these results, we assume formation of an

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acetophenone anion which is subsequently methylated by the selenonium salt.

This methylation can be avoided by generating the α-selenonio alkylide prior to addition of acetophenone. For instance, we were able to obtain 1-methyl-1-phenyloxirane in 30% yield (not optimized) by reaction with $LiCHCl_2$ in dimethyl ether at −78 °C[11]. Surprisingly, however, other reaction conditions (different temperatures, solvents, and bases) for selenonium salts *(1a)* and *(1b)* led to differing products, which we are currently investigating.

Experimental:

Alkyldiphenylselenonium tetrafluoroborates (1b)—(1d)

$AgBF_4$ (5 g, 0.026 mol) is added slowly (under N_2, at 20 °C) to a solution of diphenyl selenide (6 g, 0.026 mol) in alkyl iodide (or bromide) (0.13 mol). After 2 h, the mixture is shaken with CH_2Cl_2 (200 ml) and the silver iodide is filtered off. The CH_2Cl_2 is evaporated *in vacuo* and the residue [*(1b)—(1d)*] washed with ether (3 × 50 ml) and recrystallized.

Oxiranes (3)

A solution of potassium *tert*-butoxide (0.0075 mol) in DMSO (10 ml) is added slowly at 20 °C to a solution of a selenonium salt *(1)* (0.009 mol) and a carbonyl compound (0.006—0.007 mol) in DMSO (10 ml). After 2 h, the mixture is hydrolyzed and extracted with ether (3 × 100 ml). The ethereal fractions were dried and evaporated and the residue [*(3)*] was purified by vacuum distillation or TLC (silica gel, ether/pentane 1:9).

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[1] *D. Lloyd* and *M. I. C. Singer*, Chem. Commun. *1967*, 390.

[2] *E. Ernstbrunner* and *D. Lloyd*, Liebigs Ann. Chem. *753*, 196 (1971).

[3] *E. D. Hughes* and *K. I. Kuriyan*, J. Chem. Soc. *1935*, 1609.

[4] *N. N. Magdesieva, R. A. Kandgetiyan*, and *A. A. Ibragimov*, J. Organometal. Chem. *42*, 399 (1972).

[5] *W. W. Lotz* and *J. Gosselck*, Tetrahedron *29*, 917 (1973).

[6] *Houben-Weyl*: Methoden der organischen Chemie. Thieme-Verlag, Stuttgart 1955, Vol. 9, p. 1034.

[7] *A. H. Blatt*, Org. Synth. *2*, 239 (1969).

[8] Diphenyl selenide is inert toward alkyl iodide in the absence of silver tetrafluoroborate; cf. ref. [6], p. 1099.

[9] On reaction of *(1d)* with benzaldehyde, most of the aldehyde was recovered unchanged. This reaction is to be further investigated.

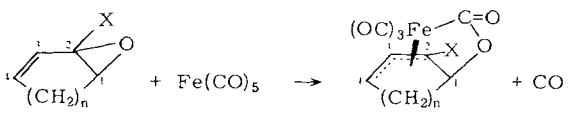
[10] *E. J. Corey* and *M. Chaykovsky*, J. Amer. Chem. Soc. *87*, 1353 (1965).

[11] *E. J. Corey* and *W. Oppolzer*, J. Amer. Chem. Soc. *86*, 1899 (1964); Tetrahedron Lett. *1967*, 2325.

Lactones and Lactams by Light-Induced Reaction of 2-Vinyloxiranes and 2-Vinylaziridines with Pentacarbonyliron—Insertion of Carbon Monoxide into an Iron-Nitrogen σ Bond[1]

By *Rudolf Aumann, Klaus Fröhlich*, and *Horst Ring*[*]

On light-induced reaction with pentacarbonyliron vinylcyclopropane systems give both carbonyliron complexes possessing an intact cyclopropane ring and 1,2,3,6-η-hexenediyl-6-one-$Fe(CO)_3$ derivatives resulting from cleavage of the cyclopropane ring and insertion of carbon monoxide[2, 3]. 2-Vinyloxiranes *(1)* or 2-vinylaziridines *(5)*, on the other hand, afford high yields of pale yellow lactones *(2)* or lactams *(6)* on photolysis (2—5% solution; 125-W Hg high pressure lamp, Duran filter; 20 °C; 2 h duration) with $Fe(CO)_5$ in benzene.



(1) *(2)*

(a): X = H; 2H instead of $(CH_2)_n$
(b): X = CH_3; 2H instead of $(CH_2)_n$
(c): X = H; n = 1
(d): X = H; n = 2

The products were isolated by fractional crystallization from benzene/hexane and their structures determined by ^{1}H-NMR (double resonance, computer simulation; cf. Fig. 1), IR, mass spectra, and elemental analysis.

Table 1. Lactones *(2)* obtained by light-induced reaction of vinyloxiranes *(1)* with $Fe(CO)_5$.

Product	Yield [%]	M. p. [°C]	*m/e*	$\nu_{(M)-C\equiv O}$ O [a] [cm^{-1}]	$\nu_{C=O}$ [b] [cm^{-1}]
(2a) [4]	90	120	238	2082, 2011, 1996	1652
(2b)	89	101	252	2078, 2005, 1992	1656
(2c)	48	107 (dec.)	250	2073, 2003, 1993	1650
(2d)	60	80 (dec.)	264	2072, 2002, 1993	1630

[a] In hexane; [b] in KBr.

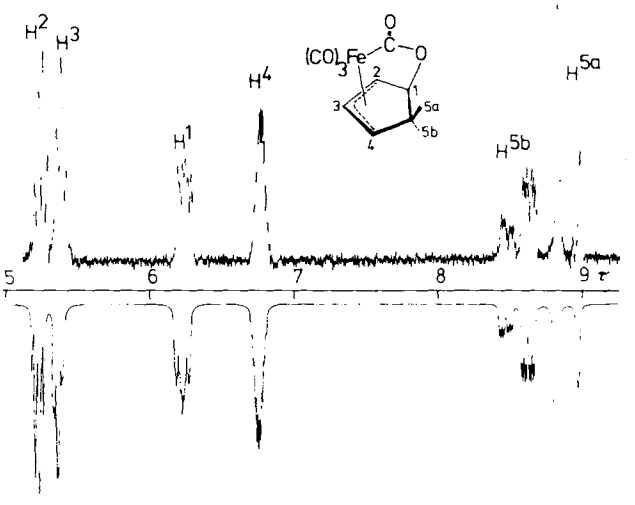
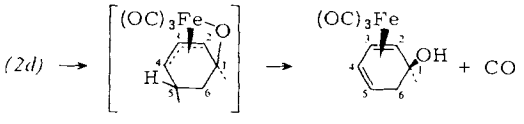


Fig. 1. Simulated and measured ^{1}H-NMR spectrum of *(2c)* (C_6H_6 solution, 100 MHz, 25 °C, TMS internal standard).

(2d) rapidly decomposes on warming—presumably *via (3d)*—undergoing loss of CO and 1,5-H migration to give *endo*-hydroxycyclohexadiene-$Fe(CO)_3$ *(4d)* (86%; m. p. 94 °C; lit.: 95 °C[5]).



(3d) *(4d)*

The light-induced reaction of vinylaziridine *(5)* with $Fe(CO)_5$ in benzene furnishes the lactam *(6)* $C_{10}H_9FeNO_6$ [71%;

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m/e 295; pale yellow crystals from benzene/hexane, m.p. 94—95°C (dec.); IR: $\nu_{(M)-C\equiv O}$ (hexane) 2080, 2023, 2007; bridging carbonyl (CH_2Cl_2) 1757 cm^{-1}; ester carbonyl (CH_2Cl_2) 1659, 1712 cm^{-1}; ^{1}H-NMR ($CDCl_3$): $H^1=6.12$, $H^2=5.49$, $H^3=5.07$, $H^{4\,syn}=6.20$, $H^{4\,anti}=7.05$, $CH_3=6.29\,\tau$].

At 60 °C, *(6)* decomposes quantitatively within 20 min with loss of one equivalent of CO to form a 2:1 mixture of the compounds *(7a)* and *(7b)* $C_9H_9FeNO_5$ [*m/e* 267; yellow crystals from hexane, m.p. 76—78 °C (dec.); IR: $\nu_{(M)-C\equiv O}$ (hexane) 2092, 2042, 2007, and 2088, 2037, 2007 cm^{-1}; ester carbonyl (CH_2Cl_2) 1657 cm^{-1}; ^{1}H-NMR: see Fig. 2].

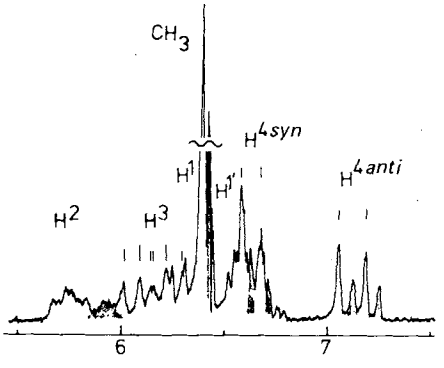
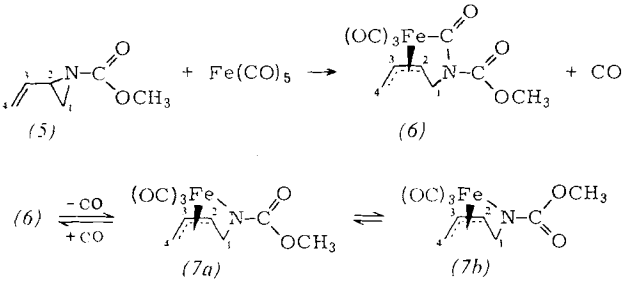


Fig. 2. ^{1}H-NMR spectrum of *(7a)/(7b)* at 10 °C (C_6H_6 solution, 100 MHz, TMS internal standard). The shaded peaks could be assigned to the isomer present in lower concentration in the equilibrium mixture.

^{1}H-NMR measurements indicate rapid interconversion of *(7a)*⇌*(7b)* with $\Delta G^{\neq}$ approximately 17 kcal/mol as estimated from coalescence of the resonance signals $H^{4\,anti}$ *(7a)*⇌$H^{4\,anti}$ *(7b)* (Fig. 2). In a CO atmosphere (70 atm; 25 °C; 50 h; benzene solution), *(7a)/(7b)* quantitatively regenerates *(6)*.



To our knowledge this constitutes the first proof of insertion of carbon monoxide into an Fe—N σ bond by isolation of the reaction products.

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[1] Reactions of Strained CC Single Bonds with Transition Metals, Part 6. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 5: ref. [2].

[2] *R. Aumann*, J. Organometal. Chem. *66*, C 6 (1974); *R. Aumann*, J. Amer. Chem. Soc., in press.

[3] *R. Aumann*, Angew. Chem. *83*, 175, 176, 177 (1971); Angew. Chem. internat. Edit. *10*, 188, 189, 190 (1971).

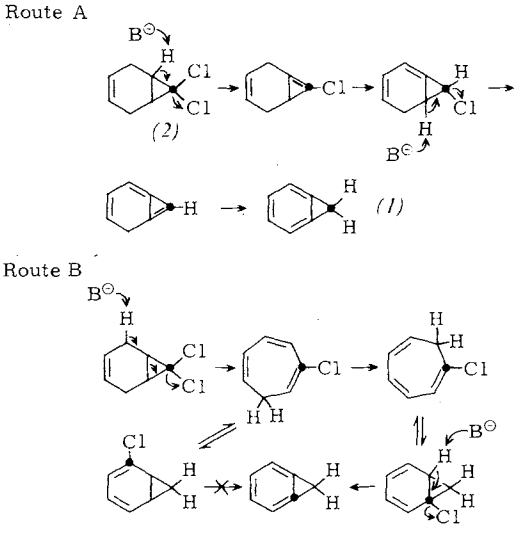
[4] Prepared by an independent route by *H. D. Murdoch*, Helv. Chim. Acta *47*, 936 (1964), and by *R. F. Heck* and *C. R. Boss*, J. Amer. Chem. Soc. *86*, 2580 (1964).

[5] *A. J. Birch, P. E. Cross, J. Lewis, D. A. White*, and *S. B. Wild*, J. Chem. Soc. *A 1968*, 332.

^{12}C Labeling for the Elucidation of Reaction Mechanisms—Benzocyclopropene Formation[**]

By *Jörn Prestien* and *Harald Günther*[*]

Two mechanisms have been proposed for the formation of benzocyclopropene (1,3,5-norcaratriene) *(1)* on basic dehydrochlorination of 7,7-dichlorobicyclo[4.1.0]hept-3-ene *(2)*[1,2]:



Since only path B involves skeletal rearrangement, carbon labeling in combination with ^{13}C-NMR spectroscopy should provide a method of distinguishing between the two routes. With this in mind we have prepared [7-^{12}C]-*(2)* from [^{12}C,D]-chloroform[3] and subjected it to dehydrohalogenation by the known procedure[1]. Figure 1 compares the ^{13}C-NMR spectra (a) and (b) of the product having natural isotope abundance[4] and labeled *(1)*, respectively. Within the error limits (*ca.* 10%), we find the same integral for the signals

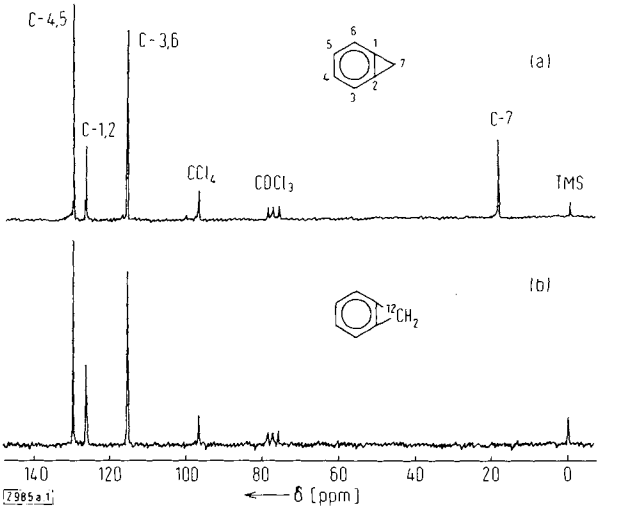


Fig. 1. PFT ^{13}C-NMR spectrum of benzocyclopropene (a) and of [7-^{12}C]-benzocyclopropene (b); 4096 accumulations in each case. Concentration *ca.* 1.1 M in $CCl_4/CDCl_3$ (3:2); tetramethylsilane as internal reference.

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[**] Applications of ^{13}C-NMR Spectroscopy, Part 14. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 13: *G. Jikeli, W. Herrig*, and *H. Günther*, J. Amer. Chem. Soc. *96*, 323 (1974).

of the aromatic C atoms: (a) 1.00 : 0.25 : 0.87; (b) 1.00 : 0.28 : 0.81. More detailed evidence comes from the fact that no signal is observed for C-7 in spectrum (b). Hence the reaction gives $\geq 95\%$ of [7-^{12}C]-*(1)* so that path B can be ruled out.

The technique of ^{12}C labeling, to our knowledge used here for the first time in the elucidation of reaction mechanisms, has a number of advantages compared to ^{13}C labeling: 1) No complications due to ^{13}C—^{13}C coupling occur; 2) in the absence of scrambling, as in the present case, the evaluation of the experiment is independent of the relatively inaccurate integration of the ^{13}C signals; 3) [^{12}C]-chloroform (isotopic purity >99.95%) currently costs 80 times less than [^{13}C]-chloroform (isotopic purity 90%).

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[1] *W. E. Billups, A. J. Blakeney,* and *W. Y. Chow,* J. C. S. Chem. Comm. *1971,* 1461.

[2] *B. Halton,* Chem. Rev. *73,* 113 (1973).

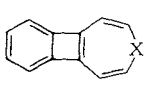
[3] Purchased from E. Merck, Darmstadt.

[4] For assignment, see *H. Günther, G. Jikeli, H. Schmickler,* and *J. Prestien,* Angew. Chem. *85,* 826 (1973); Angew. Chem. internat. Edit. *12,* 762 (1973).

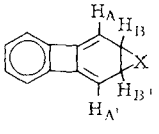
2,3-Epoxybiphenylene—A New Arene Oxide[**]

By *Günther Jikeli* and *Harald Günther*[*]

NMR spectroscopic studies in the biphenylene series[1] and other experimental findings[2, 3] suggest that of the valence isomers *(1)* and *(2)* the latter is stable since exocyclic double



(1)



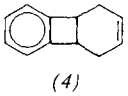
(2)
(2a), X = O



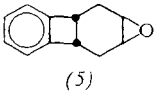
(3)

bonds on the four-membered ring should permit a better bond delocalization in the benzene ring. The *o*-phenylene structure should therefore prove suitable for the stabilization of short-lived dienes of type *(3)* having X = CH_2, C=O, NR, O, or S.

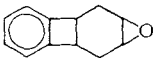
We have successfully applied this principle for the first time to the synthesis of 2,3-epoxybiphenylene *(2a)*. Starting from 1,4,4a,8b-tetrahydrobiphenylene *(4)*[4], prepared[5] from 1,3-butadiene and benzocyclobutadiene *in statu nascendi*[6], reaction with *m*-chloroperbenzoic acid in $CHCl_3$ gave 79% of a 9 : 1 mixture of the isomeric epoxides *(5)* and *(6)* for which we assume the *syn* and *anti* configuration respectively on the basis of NMR experiments with shift reagents.



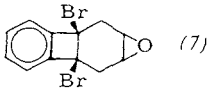
(4)



(5)



(6)



(7)

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[**] This work was supported by the Deutsche Forschungsgemeinschaft.

Compound *(5)* (m.p. 61.0—61.5 °C) was brominated with *N*-bromosuccinimide to give 45% of the dibromide *(7)* (m.p. 139—140°C) after chromatography on silica gel, whose dehydrobromination with potassium *tert*-butoxide in THF/DMSO at −3 °C under argon was complete within 15 min. Rapid work-up in an alkaline medium and crystallization (−78 °C) from pentane afforded *(2a)*, which was further purified by recrystallization from acetone at 10 °C; yield 47%, colorless crystals, m.p. ≥75 °C (decomp.).

The structure of *(2a)* follows unequivocally from the spectra. Accurate mass determination yields $C_{12}H_8O$ (*m/e* 168.05746523). The ^{1}H-NMR spectrum contains a singlet (δ 7.24 ppm, 4H) and an AA'BB' system whose data ($\delta_{AA'}$ 6.118, $\delta_{BB'}$ 3.662 ppm, $J_{AA'} = 1.39$, $J_{AB} = 3.62$, $J_{AB'} = 0.09$, $J_{BB'} = 3.67$ Hz) are typical for the benzene oxide partial structure[7]. Expectedly, the ^{13}C-NMR spectrum displays δ(2,3) at 53.2 ppm[8], in addition to methine resonances at 109.5, 120.6, and 130.1 ppm (C-1,4, C-5,8, C-6,7) and quaternary C atoms at 145.5 and 147.4 ppm. The UV spectrum [λ_{max} (dioxane) 241 (49000), 320 (3400), 332 (6200), 349 nm (7300)[9]] resembles that of 1,2-dimethylenebenzocyclobutene[2]. The IR bands typical of the epoxide ring[10] are observed at 1250 and 850 cm^{-1}.

Pure *(2a)* can be kept for several days at −20°C under argon without decomposition, but is very sensitive to hydrolysis. The hydrolysis product is 2-hydroxybiphenylene which was identified by comparison with a sample prepared by an independent route[11].

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German version: Angew. Chem. 86, 278 (1974)

[1] *G. Jikeli,* Diplomarbeit, Universität Köln 1972.

[2] *M. P. Cava* and *M. J. Mitchell:* Cyclobutadiene and Related Compounds. Academic Press, New York 1967.

[3] *M. P. Cava* and *K. T. Buck,* J. Amer. Chem. Soc. *95,* 5805 (1973).

[4] *C. A. Matuszak* and *L. Dickson,* J. Org. Chem. *37,* 3345 (1972).

[5] This synthesis was first performed by *E. Vogel* and *F. Weyres; F. Weyres,* Diplomarbeit, Universität Köln 1964. We isolated 6a,10b-dihydrobenzo[*a*]biphenylene [12] as a by-product (5—10%).

[6] *C. D. Nenitzescu, M. Avram,* and *D. Dinu,* Chem. Ber. *90,* 2541 (1957).

[7] *H. Günther, R. Schubart,* and *E. Vogel,* Z. Naturforsch. *22b,* 25 (1967).

[8] *H. Günther* and *G. Jikeli,* Chem. Ber. *106,* 1863 (1973).

[9] Owing to the ready decomposition of *(2a)* the absolute values of the extinction could have an error of *ca.* 30%.

[10] *L. J. Bellamy:* The Infrared Spectra of Complex Molecules, 2nd Edit. Wiley, New York 1958.

[11] *J. M. Blatchly, J. F. W. McOmie,* and *S. D. Thatte,* J. Chem. Soc. *1962,* 5090.

[12] *M. P. Cava* and *D. R. Napier,* J. Amer. Chem. Soc. *79,* 1701 (1957).

Cyclobutanones from 1-Bromo-1-lithiocyclopropanes and Ketones[**]

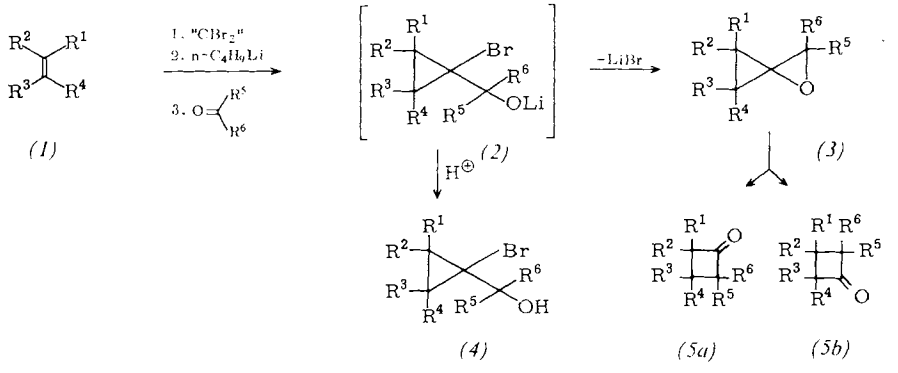
By *Manfred Braun* and *Dieter Seebach*[*]

Cyclobutanones are useful intermediates in organic synthesis[1]. Their preparation by cycloaddition of ketenes to double bonds is possible only under certain conditions[2]. We now wish to describe a new method of converting olefins *(1)* into cyclobutanones *(5)* which proceeds *via* oxaspiropentanes *(3)*. *Trost et al.* have demonstrated the synthetic utility of such epoxides prepared from other components for further interesting chemical conversions[1d].

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As starting materials we employ the readily accessible dibromocarbene adducts to olefins[3] which afford the alkoxides *(2)* by bromine-lithium exchange[4] and reaction with aldehydes and ketones below −90°C in tetrahydrofuran. On warming to room temperature the ketone adducts *(2)* eliminate lithium bromide to form the epoxides *(3)* which in some cases can be isolated when working up under basic



(1) *(2)* *(3)* *(4)* *(5a)* *(5b)*

conditions but which rearrange to the cyclobutanones *(5)* (Table 1) under acidic conditions of work-up[1d, 5]. With the aldehyde adducts *(2)* elimination is not spontaneous; the bromohydrins *(4)* are isolated (Table 1). All the new compounds exhibit the expected spectroscopic data; the physical properties of the cyclobutanones already known are in accord with literature reports[7]. It may clearly be seen from Table 1 that the olefinic component *(1)* can be varied between wide limits (mono-, 1,1- and 1,2-di-, as well as tri- and tetra-substituted).

We are currently studying the reactions of the epoxides *(3)* and cyclobutanones *(5)* for the preparation of substituted lactones[1] and vinylcyclopropanol derivatives[1d] (→cyclopentanones[1d] and dienes[8]): All these types of conversions are recorded in the literature and in essence represent functionalizations of the double bond of *(1)* with C—C linking.

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Table 1. Yields of bromohydrins *(4)* [a] and cyclobutanones *(5)* [b] based on the amount of dibromocyclopropane employed [obtained from *(1)* and "CBr_2"].

R^1	R^2	R^3	R^4	R^5	R^6	Yields [%] *(4)* [a]	*(5)* [b]
H	H	H	n-$C_{10}H_{21}$	CH_3	CH_3		70
H	H	CH_3	CH_3	C_6H_5	C_6H_5		95
H	—$(CH_2)_4$—		H	—$(CH_2)_5$—			40
H	—$(CH_2)_4$—		H	C_6H_5	C_6H_5		85
H	—$(CH_2)_4$—		H	H	n-C_4C_9	85	
H	—$(CH_2)_4$—		H	H	C_6H_5	87 [6]	
H	CH_3	CH_3	CH_3	C_6H_5	C_6H_5		70
CH_3	CH_3	CH_3	CH_3	CH_3	CH_3		58
CH_3	CH_3	CH_3	CH_3	C_6H_5	C_6H_5		90
CH_3	CH_3	CH_3	CH_3	—CH=CH—$(CH_2)_3$—			35
CH_3	CH_3	CH_3	CH_3	H	n-C_4H_9	80	
CH_3	CH_3	CH_3	CH_3	H	C_6H_5	84	

[a] Hitherto only one compound of this type has been described: *K. G. Taylor et al.*, J. Org. Chem. *37*, 2437.
[b] *(5a)* and *(5b)* differ only in the products of lines 1, 2, and 7 of this Table. We have not yet separated the analytically pure mixtures obtained in these cases; one isomer strongly predominates (cf. refs. [5, 7]).

[1] a) Baeyer-Villiger oxidation of four-membered cyclic ketones to γ-lactones; *S. L. Friess* and *P. E. Frankenburg*, J. Amer. Chem. Soc. *74*, 2679 (1952); *E. J. Smutny* and *J. D. Roberts*, *ibid.* *77*, 3420 (1955); *H. Bestian* and *D. Günther*, Angew. Chem. *75*, 841 (1963); Angew. Chem. internat. Edit. *2*, 608 (1963); *D. C. Dittmer et al.*, Chem. Ind. (London) *1964*, 152; and refs. [1b—1d]; b) *E. J. Corey*, *Z. Arnold*, and *J. Hutton*, Tetrahedron Lett. *1970*, 307; c) *Y. Tsuda*, *T. Tanno*, *A. Ukai*, and *K. Isobe*, *ibid.* *1971*, 2009; d) *B. M. Trost*, Fortschr. Chem. Forsch. *41*, 1 (1973), and further literature cited therein; *B. M. Trost*, *D. Keeley*, and *M. J. Bogdanowicz*, J. Amer. Chem. Soc. *95*, 3068 (1973).

[2] Houben-Weyl: Methoden der organischen Chemie. Vol. IV/4, Thieme, Stuttgart 1971, pp. 180ff., and further literature cited therein; *J. Marchand-Brynaert* and *L. Ghosez*, J. Amer. Chem. Soc. *94*, 2870 (1972).

[3] a) *W. v. E. Doering* and *A. K. Hoffmann*, J. Amer. Chem. Soc. *76*, 6162 (1954); b) *M. Makosza* and *M. Fedoryński*, Synth. Commun. *3*, 305 (1973); *L. Skattebøl*, *G. Aziz Abskharoun*, and *T. Greibrokk*, Tetrahedron Lett. *1973*, 1367; c) *D. Seyferth et al.*, J. Amer. Chem. Soc. *87*, 4259 (1965).

[4] *W. R. Moore* and *H. R. Ward*, J. Org. Chem. *25*, 2073 (1960); *G. Köbrich et al.*, Angew. Chem. *79*, 15 (1967); Angew. Chem. internat. Edit. *6*, 41 (1967); *D. Seyferth* and *R. L. Lambert, Jr.*, J. Organometal. Chem. *55*, C 53 (1973).

[5] *J. R. Salaün* and *J. M. Conia*, Chem. Commun. *1971*, 1579; *D. H. Aue*, *M. J. Meshishnek*, and *D. F. Shellhamer*, Tetrahedron Lett. *1973*, 4799.

[6] In the case of *(4)*, $R^1 = R^4 = H$, $R^2—R^3 = —(CH_2)_4—$, $R^5 = H$, $R^6 = C_6H_5$, conversion into the cyclobutanone was performed by 24 hours' stirring of a benzene solution of the bromohydrin with 50% aqueous NaOH and catalytic amounts of triethyl(benzyl)ammonium chloride, *i. e.* under "*Makosza* conditions" [3b].

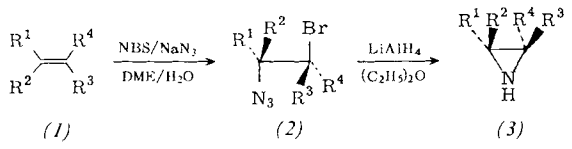
[7] *H. Staudinger* and *E. Suter*, Ber. Deut. Chem. Ges. *53*, 1092 (1920); *R. Huisgen* and *L. A. Feiler*, Chem. Ber. *102*, 3391 (1969); *R. C. Cookson*, *A. G. Edwards*, *J. Hudec*, and *M. Kingsland*, Chem. Commun. *1965*, 98.

[8] *R. J. Ellis* and *H. M. Frey*, Proc. Chem. Soc. (London) *1964*, 221; *W. R. Roth* and *J. König*, Liebigs Ann. Chem. *688*, 28 (1965).

A New Reagent for Stereospecific Synthesis of Aziridines from Olefins

By *D. Van Ende* and *Alain Krief*[*]

The increasing biological and chemical interest in polyenes bearing terminal aziridines[1] incited us to look for a general method of aziridine synthesis particularly allowing the regiospecific[2] insertion of a nitrogen moiety in the terminal olefinic part of a polyolefin.



(1) *(2)* *(3)*

Scheme 1.

In this paper we report an aziridine synthesis from monoolefins *(1)* which proceeds according to Scheme 1. We first obtained azido β-bromo compounds *(2)* (Table 1) by addition of a new reagent[4], prepared *in situ* from *N*-bromosuccinimide (NBS) and NaN_3, to a suspension of an olefin in dimethoxyethane (DME)/H_2O (see experimental procedure). We found that our reagent, unlike *Hassner*'s bromine azide[5], can be prepared *in situ* in the presence of an olefin, and can be used in aqueous medium without significant hydrolysis[6]. This reagent adds Br/N_3 units directiospecifically[2,7] to the carbon-carbon double bond (according to the Markownikoff rule). Suitable olefins include citronellyl acetate *(1a)*, citronellyl benzoate *(1b)*, (*E*)-3-methyl-2-pentene *(1c)*, (*Z*)-3-methyl-2-pentene *(1d)*.

Table 1. α-Azido β-bromo derivatives *(2)* prepared.

Cpd.	R^1	R^2	R^3	R^4	Yield [%]
(2a)	CH_3	CH_3	H	$-(CH_2)_2-CH(CH_3)-(CH_2)_2-OCOCH_3$	65
(2b)	CH_3	CH_3	H	$-(CH_2)_2-CH(CH_3)-(CH_2)_2-OCOC_6H_5$	65
(2c)	CH_3	H	C_2H_5	CH_3	55
(2d)	CH_3	H	CH_3	C_2H_5	55
(2e)	CH_3	H	H	n-C_5H_{11}	65
(2f)	CH_3	H	n-C_5H_{11}	H	65
(2g)	H	H	H	n-C_6H_{13}	13

In the last two cases addition proceeds *trans* stereospecifically[8]; *trans* addition is also observed on reaction of *cis*-2-octene *(1e)* and *trans*-2-octene *(1f)*. As in other electrophilic additions, trisubstituted olefins react faster with Br/N_3 than do di- or monosubstituted ones. The low yield of 2-azido-1-bromooctane *(2g)* seems to be the consequence of this low reactivity.

The desired aziridines *(3)* are obtained in fair yield (60—70%) by $LiAlH_4$-mediated cyclization[9] of the azido β-bromo compounds *(2)*. This reaction proceeds stereospecifically.

7-Azido-6-bromo-3,7-dimethyloctyl acetate (2a)[10]

N-Bromosuccinimide (NBS) (623 mg, 3.5 mmol) was added in small portions to a precooled (−5°C) suspension prepared by mixing a DME (16 ml) solution of citronellyl acetate *(1a)* (500 mg, 2.5 mmol) with an NaN_3 (812 mg, 12.5 mmol) aqueous solution (4 ml). The initial yellow color observed faded away after each addition. When all the NBS was consumed, the reaction mixture was allowed to stand (0.5 h, 0°C), then extracted with pentane and purified by preparative layer chromatography[10,11] to give *(2a)* in 65% yield.

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[1] a) *E. J. Corey, P. R. Ortiz de Montellano, K. Lin,* and *P. D. G. Dean,* J. Amer. Chem. Soc. *89*, 2797 (1967); b) *L. M. Riddiford, A. M. Ajami, E. J. Corey, H. Yamamoto,* and *J. E. Anderson, ibid. 93*, 1816 (1971).

[2] *Directio* [3] refers to the making or breaking of different bonds at a specific part of a molecule; *regio* refers to making or breaking of the same kind of bond at different possible parts of the same molecule.

[3] *H. G. Viehe* and *S. Y. Delavarenne,* Chem. Ber. *103*, 1198 (1970).

[4] For regiospecific Br/N_3 introduction into the terminal part of polyolefins, see *D. Van Ende and A. Krief,* Angew. Chem. *86*, 311 (1974); Angew. Chem. internat. Edit. *13*, 279 (1974).

[5] *A. Hassner* and *F. P. Boerwinkle,* J. Amer. Chem. Soc. *90*, 216 (1968); *A. Hassner,* Accounts Chem. Res. *4*, 9 (1971).

[6] *D. A. Spencer,* J. Chem. Soc. *1925*, 127.

[7] The 7-azido-6-bromocitronellyl acetate obtained by our method (contaminated by less than 5% of its directioisomer) is identical (^{1}H-NMR) with a sample prepared according to ref. [5] which contained 13% of the directioisomer.

[8] Compounds *(2c)* and *(2d)* were free from stereoisomer. The stereochemical purity was checked by comparison of the ^{1}H-NMR spectra of *(2c)* and *(2d)* with that of the known 30/70 *(2c)/(2d)* mixture.

[9] Reaction conditions: 50-fold excess of $AlLiH_4$ in ether, the crude product was purified by preparative layer chromatography (SiO_2 Merck, 2 mm, methanol/ether), and *(3)* was extracted with *methanol.*

[10] NBS reerystallized from water; DME peroxide free; preparative layer chromatography (SiO_2 Merck, 2 mm, ether/pentane 3:7).

[11] Unidentified compounds (10%, R_f 0.35) and 6-bromo-7-hydroxycitronellyl acetate (10%, R_f 0.26) were also separated. Lower NaN_3 concentrations in the aqueous solution (1—2 mol/l) or lower NBS/NaN_3 ratios (1:1 or 1:2) favor formation of the corresponding bromohydrin.

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A Highly Potent Reagent for Regioselective and Stereospecific Synthesis of Polyenes Bearing Terminal Aziridine Groups

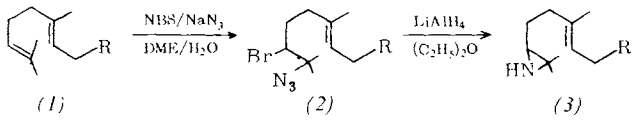
By *D. Van Ende* and *A. Krief*[*]

The only recorded regioselective syntheses of molecules such as 2,3-epiminosqualene[1] and the 2,3-epimino analog of the *Cecropia* juvenile hormone[2] are due to *Corey*; however, these syntheses suffer from low overall yields due to multistep reactions.

In this paper we report a new method of introducing a nitrogen moiety into the terminal carbon-carbon double bond of polyolefins, particularly those in which all the double bonds are trisubstituted and more or less equally sterically encumbered (Scheme 1). We studied the behavior of different nitrogen-introducing reagents, in various solvent systems, towards three polyolefins, namely geranyl acetate *(1')*, farnesyl acetate *(1'')*, and squalene *(1''')*.

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Scheme 1.

In the most successful cases, regioselective conversion of these polyolefins to their terminal azido β-bromo derivatives (Table 1) was achieved by treatment of a suspension of the polyolefin in dimethoxyethane (DME)/water with *N*-bromosuccinimide (NBS) in the presence of sodium azide. These reaction conditions were optimized for monoolefins[3].

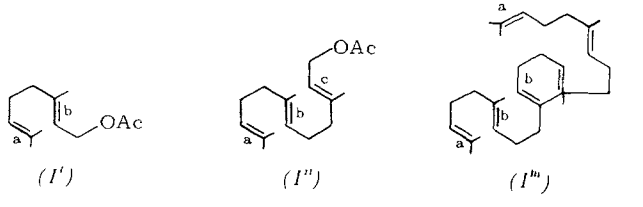


Table 1. α-Azido β-bromo compounds *(2)* and aziridines *(3)*.

Starting polyolefin *(1)*	recovered [%]	*(2)* Yield [%] [a]		*(3)* Yield [%] [b]	
(1')	10	*(2'a)*	70	*(3'a)*	60
		(2'b)	0		
(1'')	20	*(2''a)*	60	*(3''a)*	75
		(2''b)	3		
		(2''c)	0		
(1''')	30	*(2'''a)*	24	*(3'''a)*	75
		(2'''b)	4.5	*(3'''b)*	75
		[4]			

[a] Based on reacted *(1)*.
[b] Based on starting amount of *(2)*.

The structural assignment and regioisomeric purity of each compound were established by ^{1}H-NMR and mass spectral data. All the described α-azido β-bromo derivatives were cyclized to the desired corresponding aziridines *(3)*[5] in fair yields (Table 1) by use of $LiAlH_4$. The structures proposed for aziridines derived from *(2'a)* and *(2''a)* were corroborated by the identity of their IR, ^{1}H-NMR, and mass spectra with those of authentic samples[1, 2].

It is interesting to note that when polyolefins *(1'')* and *(1''')*[6] were treated by a conventional reagent (*i.e.* BrN_3 in CH_3NO_2/CH_2Cl_2) in the absence of water (reaction conditions proposed by *Hassner* in the case of monoolefins)[7] low yields of azido β-bromo derivatives and very little terminal preference were observed[8].

To account for the high terminal selectivity of our new reagent, as opposed to the low regioselectivity of BrN_3, we assume that in our "heterogeneous, highly polar medium (DME/H_2O) the coiled polyolefins would selectively present their terminal olefinic part to the attack of the extensively solvated bromonium ion"[9].

In conclusion, to illustrate the potential of our new reagent, we would point out that our two-step synthesis affords a 48% overall yield of epiminofarnesol *(3''a)* compared to the 15% yield obtained in the previously published five-step synthesis[2].

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[1] *E. J. Corey, P. R. Ortiz de Montellano, K. Lin,* and *P. D. G. Dean,* J. Amer. Chem. Soc. *89*, 2797 (1967).

[2] *L. M. Riddiford, A. M. Ajami, E. J. Corey, H. Yamamoto,* and *J. E. Anderson,* J. Amer. Chem. Soc. *93*, 1816 (1971).

[3] *D. Van Ende* and *A. Krief,* Angew. Chem. *86*, 311 (1974); Angew. Chem. internat. Edit. *13*, 279 (1974).

[4] A mixture of all possible diazido dibromo derivatives was also obtained (11% yield). IR, ^{1}H-NMR, and mass spectra confirmed the proposed structures.

[5] For experimental procedure, see ref. [3].

[6] With geranyl acetate, this reagent gave 7-azido-6-bromogeranyl acetate in 30% yield; no regioisomer was formed.

[7] *A. Hassner,* Accounts Chem. Res. *4*, 9 (1971).

[8] For a *non-regioselective* introduction of IN_3 into squalene, see *L. Avruch* and *A. C. Oehlschlager.* Synthesis *1973*, 622.

[9] *E. E. Van Tamelen* and *K. B. Sharpless,* Tetrahedron Lett. *1967*, 2655.

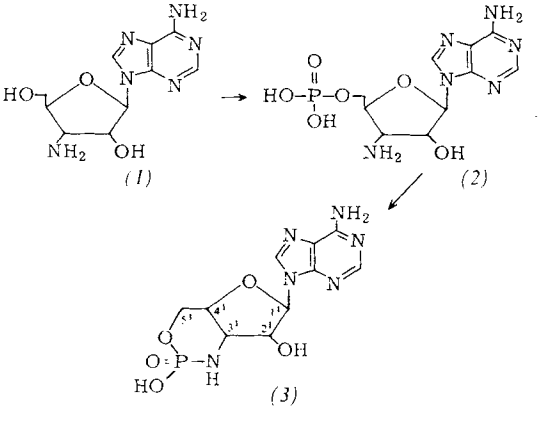
Synthesis of 3'-Amido-3'-deoxyadenosine 3',5'-Cyclophosphate[***]

By *Michael Morr, Maria-Regina Kula, Georg Roesler,* and *Bernd Jastorff*[*]

Comparative studies on synthetic derivatives of adenosine 3',5'-cyclophosphate (cAMP)[1] have shown the biological properties of cAMP to be very strongly influenced by modification of the phosphate ring[2].

Position 3' is most sensitive: thus replacement of the oxygen by a methylene group leads to complete loss of biological activity[3]. We synthesized the 3'-amido-3'-deoxy analog *(3)* of cAMP in order to determine whether replacement of the oxygen by an NH group has a similar pronounced effect on properties.

Starting from 3'-amino-3'-deoxyadenosine *(1)* isolated from the culture filtrate of *Helminthosporium* sp 215[4, 5] we obtained the 5'-phosphate *(2)* either by chemical phosphorylation with $POCl_3$/triethyl phosphate[6] or by preparative enzymatic phosphorylation with adenosine kinase (E.C. 2.7.1.2.0)[7]. Cycliza-



tion of the triethylammonium salt of *(2)* to give the cAMP analog *(3)* was performed with dicyclohexylcarbodiimide in dimethylformamide/*tert*-butanol/water.

Compound *(3)* was unequivocally characterized by chromatographic comparison with cAMP and isomeric 5'-amido-5'-

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deoxy-cAMP[2] and by chemical and enzymatic degradation. Both acid-treatment and incubation with cAMP-specific phosphodiesterase from bovine heart (E.C. 3.1.4.1) led to the 5'-phosphate *(2)* which was then dephosphorylated to the starting compound *(1)* by treatment with 5'-nucleotidase.

The 3'-N—P bond in *(3)* possesses a considerably greater chemical stability (no hydrolysis after 5 h at pH 7 and 37 °C) than the 5'-N—P bond in 5'-amido-5'-deoxy-cAMP[2].

Preliminary biological investigations have shown that *(3)* is a substrate for bovine heart cyclophosphodiesterase and also competes with cAMP for binding sites on protein kinases from bovine brain and rabbit muscle, thus activating these enzymes[8].

3'-Amido-3'-deoxyadenosine 3',5'-cyclophosphate (3)

Compound *(2)* (130 mg, 0.3 mmol) is mixed with triethylamine (0.8 ml), dimethylformamide (15 ml), *tert*-butanol (15 ml), water (7 ml), and dicyclohexylcarbodiimide (618 mg, 3 mmol) and heated to 100 °C for 8 h. After cooling, dicyclohexylurea is filtered off and the solution is evaporated down in an oil-pump vacuum. The residue is extracted with ether (4 × 30 ml) and subsequently treated with water. After filtration the filtrate is concentrated and adjusted to pH 7.5 prior to being poured onto a QAE A25 Sephadex column (HCO_3 form). After washing of the column with water elution was performed with a linear gradient of water and 0.1 M triethylammonium hydrogen carbonate (pH 7.5). The eluate was continuously monitored at 253 nm and collected in fractions. The main fraction was concentrated, stripped three times with ethanol, and subsequently lyophilized from water. The procedure yielded 50 mg of *(3)* (40% yield).

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[1] For a review, see *R. K. Robins, L. N. Simon*, and *D. A. Shuman*, Advan. Cycl. Nucleotide Res. *3* (1974), in press.

[2] *B. Jastorff* and *H. P. Bär*, Eur. J. Biochem. *37*, 497 (1973).

[3] *J. F. Kuo* and *P. Greengard*, Biochem. Biophys. Res. Commun. *40*, 1032 (1970).

[4] *N. N. Gerber* and *H. A. Lechevalier*, J. Org. Chem. *27*, 1731 (1962).

[5] We are grateful to Dr. *N. Gerber* for kindly providing the fungus, and to Prof. *F. Wagner*, Dr. *H. Vogelmann*, and Mr. *D. Pape*, Stöckheim, for the fermentation and isolation of 3'-amino-3'-deoxyadenosine *(1)*.

[6] *M. Morr* and *M.-R. Kula*, Tetrahedron Lett. *1974*, 23.

[7] *G. Roesler*, Göttingen, unpublished results, 1973.

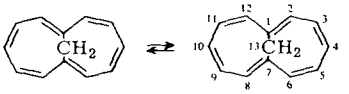
[8] For details, see *N. Panitz, E. Rieke, M. Morr, K. G. Wagner, G. Roesler*, and *B. Jastorff*, to be published.

1,7-Methano[12]annulene—the 12π Analog of 1,6-Methano[10]annulene

By *Emanuel Vogel, Heinrich Königshofen, Klaus Müllen*, and *Jean F. M. Oth*[*]

Dedicated to Professor Heinrich Hellmann on the occasion of his 60th birthday

That 1,6-methano[10]annulene[1] possesses aromatic character, while the simple [10]annulenes[2]—on account of steric factors—represent reactive polyolefins, categorically underlines the significance of the concept of "bridging"[1,3] for verification of the Hückel rule in the case of the neutral 10π electron system. Moreover, it would appear that this concept could be used as a basis for studies aimed at providing experimental evidence in support of our present ideas on the nature of 4nπ electron systems[4].



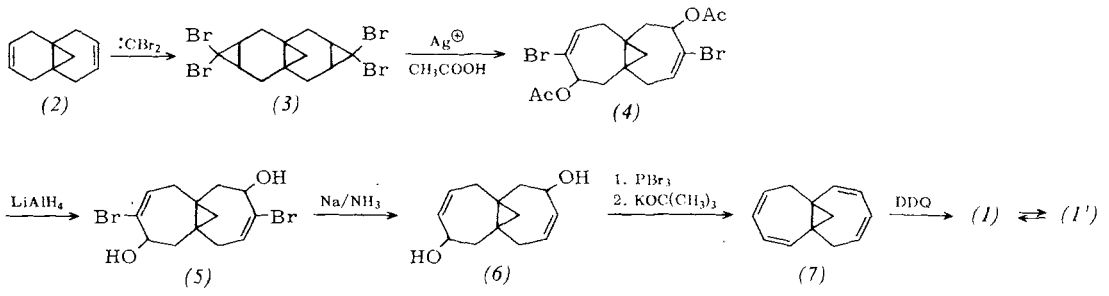
(1) *(1')*

Our particular interest centered on 1,7-methano[12]annulene *(1)*, since the geometry of the ring skeleton of this hydrocarbon corresponds to that of the 1,6-methano[10]annulene and may therefore be regarded as its 12π analog[5]. According to molecular models the peripheral annulene ring of *(1)* is only slightly puckered, whereas the unbridged [12]annulene[6], which has a configuration with alternating *cis*- and *trans*-double bonds, exhibits strong angular deformation due to steric interactions of the inner hydrogen atoms. In agreement with geometrical considerations, we have found that the 1,7-methano[12]annulene—as distinct from the [12]annulene parent compound[7]—exhibits all the properties to be expected of a 4nπ system. *(1)* can be prepared from the readily accessible tricyclo[4.4.1.$0^{1,6}$]undeca-3,8-diene *(2)*[1]. Reaction of the diene with bromoform, triethylbenzylammonium chloride, and 50% sodium hydroxide according to the method of *Makosza et al.*[8] afforded the 2:1 dibromocarbene adduct *(3)* (m.p. 169—170 °C; yield 59%), whose outer cyclopropane rings are *anti* to the central cyclopropane ring. Treatment of *(3)* with silver acetate in boiling glacial acetic acid (100 h) results in formation of a mixture of 4,10-dibromo-5,11-diacetoxytricyclo-[5.5.1.$0^{1,7}$]tridecadienes (yield *ca.* 50%)[9], from which a homogeneous isomer of probable structure *(4)* (m.p. 200—202 °C; yield 15%) can be isolated by fractional crystallization from ethyl acetate. *(4)* was then converted into the diol *(6)* (m.p. 189—191 °C; yield 50%); this was achieved by first removing the acetate groups by reduction with $LiAlH_4$ in tetrahydrofuran and then treating the crude *(5)* so obtained in tetrahydrofuran solution with sodium in liquid ammonia (−78 °C).

Attempts to dehydrate *(6)* proved unsatisfactory. *(6)* was therefore converted by treatment with phosphorus tribromide into the dibromide (m.p. 152—153 °C; yield 36%), which, on treatment with potassium *tert*-butoxide in tetrahydrofuran (0 °C), could be readily dehydrobrominated to the tetraene *(7)* and its isomers [b.p. 56—59 °C/0.4 torr (mixture); yield 27%] having mirror-image arrangement of the conjugated double bonds. That *(7)* and the aforesaid isomers are present, follows from the NMR spectra (a singlet for each of the cyclopropane protons). Separation of the readily autoxidizable hydrocarbon mixture was unnecessary. The same dehydrogenating agent, 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ), as was used in the synthesis of bridged [10]- and [14]annulenes could also be employed here; however, it was necessary to heat the tetraene mixture with the quinone in boiling anisole (165 °C) for 1/2 h. Chromatography on silica gel afforded *(1)* as a reddish brown liquid (b.p. 72—74 °C/0.2 torr; yield 39%) which crystallizes below −50 °C and is sensitive to air. Recrystallization from methanol at low temperature affords *(1)* as splendid blackish-brown needles having m.p. −6 to −4 °C.

According to CNDO—CI calculations, the UV spectrum of *(1)* [λ_{max} (cyclohexane) = 254 (ε = 54000), 263 (51000), 300 (1000, sh), 425 nm (240)] may be interpreted as that of a polyene; it resembles the UV spectra of dehydro[12]annulenes[10].

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The ^{1}H-NMR spectrum of *(1)* at room temperature, which is displayed in Figure 1 along with the spectrum of 1,6-methano[10]annulene, shows a singlet for the bridge protons at $\tau = 3.94$ and two multiplets for the annulene protons at $\tau = 4.5$ (2-H, 6-H, 8-H, 12-H) and 4.8 (3-H to 5-H, 9-H to 11-H). Remarkably, the signals of aliphatic and olefinic protons—in complete reversal of the resonance behavior in 1,6-methano[10]annulene—occur at unusually low and unusually high field respectively. *(1)* may therefore sustain a relatively strong paramagnetic ring current.

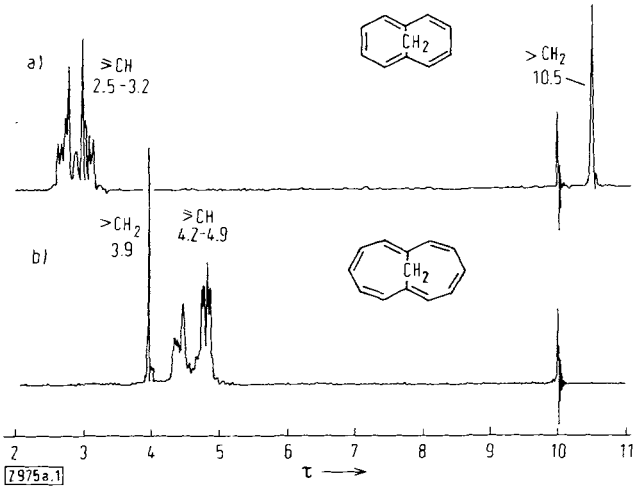


Fig. 1. 60-MHz ^{1}H-NMR spectra of a) 1,6-methano[10]annulene and b) 1,7-methano[12]annulene *(1)* (both recorded in CCl_4 at room temperature with TMS as internal standard).

The ^{1}H-NMR spectrum of *(1)* is temperature-dependent, thus indicating the presence of a rapid dynamic process. On lowering the temperature the multiplets of the annulene protons gradually broaden below *ca.* −60 °C, while the singlet of the bridge protons remains unchanged. Change of shape in the multiplet ceases at −135 °C. Analysis of the spectrum at room temperature (region of rapid exchange) and at −135 °C (no exchange)[11] clearly indicates that the dynamic process involves a π-bond shift—*i.e.* the valence tautomerism *(1)*⇄*(1')*, which confers C_{2v} symmetry on the molecule on the NMR time-scale above −60 °C. An attempt to derive the kinetic parameters of the π-bond shift from the temperature dependence of the ^{1}H-NMR spectrum met with difficulties, since the annulene protons form a strongly coupled spin system. This suggested that ^{13}C-NMR spectroscopy would have to be used to determine these parameters.

The room-temperature ^{13}C-NMR spectrum of *(1)*[12] immediately reveals the effective C_{2v} molecular symmetry induced by rapid double bond migration since it shows only four signals for the annulene C atoms, whose assignment (by partial decoupling) is to be inferred as in Figure 2a.

As can easily be seen, freezing of the π-bond shift leads to loss of magnetic equivalence of C-2 and C-6 and of C-3 and C-5. In agreement with this the 4-line ^{13}C-NMR spectrum observed at room temperature transforms between −40 and 120 °C, with broadening and subsequent splitting of the C-2/C-6 and C-3/C-5 signals into a 6-line spectrum (Fig. 2b)

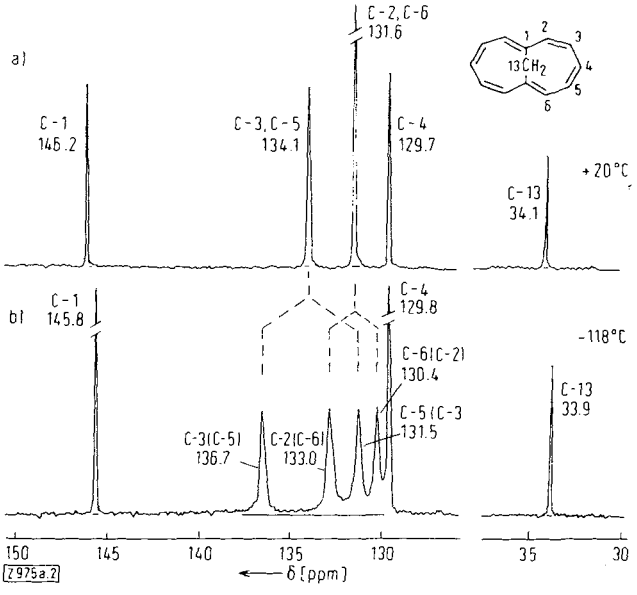
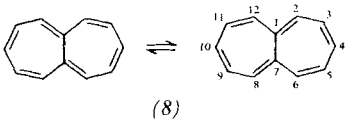


Fig. 2. ^{1}H broad band decoupled ^{13}C-NMR spectra of 1,7-methano[12]annulenes *(1)* at, a) room temperature, and b) −118 °C (in D_8-THF/CS_2 with TMS as internal standard, $\delta_{TMS} = 0$).

corresponding to that of the 1,7-methano[12]annulene with C_2 symmetry. It is possible, by means of a line-shape analysis of the signals of C-2, C-3, C-5, C-6, to derive an activation energy of 5 kcal/mol for the π bond shift. If one considers that further flattening of the peripheral annulene is enforced in the transition state of the bond shift, this value represents an upper limit for the energy difference between the 1,7-methano[12]annulene structure with delocalized and with localized π bonds[13].



(8)

Investigations on *(1)* call one's attention to the 12π system heptalene *(8)*[14,15] and the still unsatisfactorily explained bonding in this molecule. The rapid π-bond shift[15] postulated for *(8)* which so far has eluded experimental detection could also be detected ^{13}C-NMR spectroscopically[16].

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[1] For summaries see: *E. Vogel*, Spec. Publ. No. 21, The Chemical Society, London 1967, p. 113; Chimia *22*, 21 (1968); Proc. Robert A. Welch Found. Conf. Chem. Res. *12*, 215 (1968).

[2] *S. Masamune* and *N. Darby*, Accounts Chem. Res. *5*, 272 (1972); *E. E. van Tamelen, T. L. Burkoth*, and *R. H. Greeley*, J. Amer. Chem. Soc. *93*, 6120 (1971).

[3] *V. Boekelheide* and *J. B. Phillips*, J. Amer. Chem. Soc. *85*, 1545 (1963).

[4] *H. C. Longuet-Higgins*, Spec. Publ. No. *21*, The Chemical Society, London 1967, p. 109; *J. A. Pople* and *K. G. Untch*, J. Amer. Chem. Soc. *88*, 4811 (1966); *F. Sondheimer*, Accounts Chem. Res. *5*, 81 (1972).

[5] For the synthesis of the isomeric 1,6-methano[12]annulene see *E. Vogel, M. Mann, Y. Sakata, K. Müllen*, and *J. F. M. Oth*, Angew. Chem. *86*, 231 (1974); Angew. Chem. internat. Edit. *13*, 283 (1974).

[6] *J. F. M. Oth, H. Röttele*, and *G. Schröder*, Tetrahedron Lett. *1970*, 61; *J. F. M. Oth, J.-M. Gilles*, and *G. Schröder*, *ibid.* *1970*, 67; *J. F. M. Oth*, Pure Appl. Chem. *25*, 573 (1971).

[7] The π-bond shift in [12]annulene is sterically so strongly hindered that it is not detectable NMR spectroscopically at −40 C, the stability limit of the molecule [6].

[8] *M. Makosza* and *M. Wawrzyniewicz*, Tetrahedron Lett. *1969*, 4659.

[9] The yield of *(1)* can be almost doubled if the isomeric mixture is used directly for further reaction.

[10] *R. Wolovsky* and *F. Sondheimer*, J. Amer. Chem. Soc. *87*, 5720 (1965); *K. G. Untch* and *D. C. Wysocki*, *ibid.* *88*, 2608 (1966); *F. Sondheimer, R. Wolovsky, P. J. Garratt*, and *I. C. Calder*, *ibid.* *88*, 2610 (1966).

[11] Assignment of the NMR spectrum (100 MHz) at −135 C is as follows: τ = 4.53 (2-H, 8-H), 4.80 (3-H, 9-H), 4.88 (4-H, 10-H), 4.82 (5-H, 11-H), 4.39 (6-H, 12-H), and 4.02 (2 13-H); $J_{2,3} = 5.3$, $J_{3,4} = 12.2$, $J_{4,5} = 6.0$, and $J_{5,6} = 12.5$ Hz [numbering of the H atoms in accordance with *(1')*].

[12] *(1)* can be used as a model compound for clarifying the question whether a paramagnetic ring current effect exists for ^{13}C-nuclear magnetic resonance.

[13] In cyclooctatetraene the delocalized structure with D_{8h}-symmetry is more energy rich by about 4 kcal/mol than the planar structure with localized π bonds [6]; see also *F. A. L. Anet, A. J. R. Bourn*, and *Y. S. Lin*, J. Amer. Chem. Soc. *86*, 3576 (1964).

[14] *H. J. Dauben, Jr.* and *D. J. Bertelli*, J. Amer. Chem. Soc. *83*, 4659 (1961).

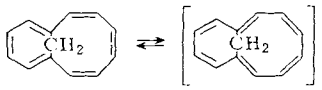
[15] *D. J. Bertelli* in: The Jerusalem Symposia on Quantum Chemistry and Biochemistry. Vol. III, p. 326 (1971); *G. Binsch*, *ibid.* p. 25; *T. Nakajima*, Fortschr. Chem. Forsch. *32*, 1 (1972).

[16] The room-temperature ^{13}C-NMR spectrum (CF_2Br_2/CD_2Cl_2) of *(8)* [numbering of C atoms analogous to *(1')*] shows four sharp signals at δ = 140.9 (C-1/C-7), 135.3 (C-2/C-6), 131.2 (C-4), and 130.7 ppm (C-3/C-5). Analogous to the behavior in *(1)*, the C-2/C-6 and C-3/C-5 signals split below −160 C (coalescence temperature); *E. Vogel, H. Königshofen, J. Wassen, K. Müllen*, and *J. F. M. Oth*, unpublished.

1,6-Methano[12]annulene

By *Emanuel Vogel, Max Mann, Yoshiteru Sakata, Klaus Müllen*, and *Jean F. M. Oth*[*]

1,6-Methano[12]annulene may exist as one of the valence tautomers *(1)* and *(2)*, or there could be equilibrium between *(1)* and *(2)*. It can easily be seen that the case of equilibrium corresponds to a π-bond shift, which as distinguished from that observed in 1,7-methano[12]annulene[1], is a non-isodynamic process[2]. According to molecular models, however, *(1)* is much more energetically favored than *(2)*, and it would seem that 1,6-methano[12]annulene ought to be present as *(1)* and not exhibit any π-bond shift.

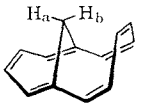


(1) *(2)*

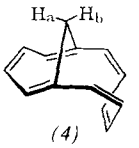
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[**] Dr. *Sakata* thanks the Alexander von Humboldt Foundation for a stipend.

(1) possesses the relatively rigid preferred conformations *(3)* and *(4)*. A feature common to both of these conformations is that the peripheral annulene ring deviates considerably more from planarity than in 1,7-methano[12]annulene. In order to establish the extent to which the properties of [12]annulenes, or [4*n*]annulenes in general, are dependent on the ring geometry[3], it was considered essential to include the examination of 1,6-methano[12]annulene in our studies.



(3)

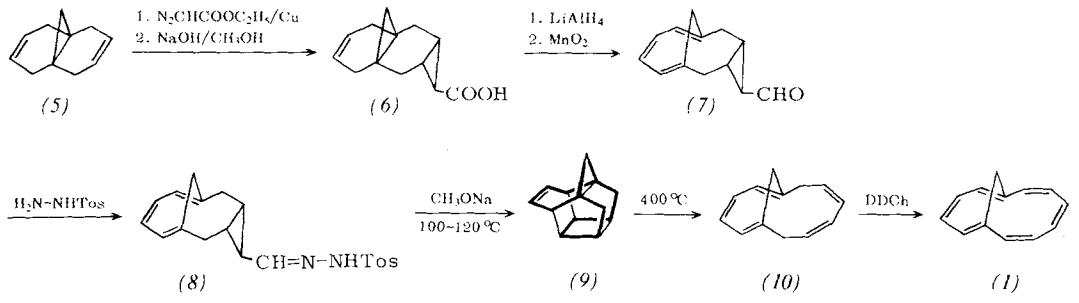


(4)

1,6-Methano[12]annulene could be synthesized in the same way as the isomeric 1,7-methano[12]annulene from tricyclo[4.4.1.$0^{1,6}$]undeca-3,8-diene *(5)*[4]. To convert *(5)* into the new [12]annulene a C_2 unit had to be added to one of the double bonds; this was achieved by Cu-catalyzed reaction with ethyl diazoacetate. An adduct mixture was formed, which on hydrolysis with methanolic sodium hydroxide afforded tetracyclo[5.4.1.$0^{1,7}$.$0^{3,5}$]dodeca-9-ene-4-*exo*-carboxylic acid *(6)* (m. p. 200—201 °C; yield 15%[5], after fractional crystallization from ethyl acetate). The configuration of *(6)* followed from a comparison of the NMR spectra of the secondary product *(7)* and its stereoisomer having an *endo* aldehyde group: only in the case of the *endo* isomer did the aldehyde group serve as a basis for the diamagnetic anisotropic effect of the cycloheptatriene moiety and therefore absorb at relatively high field strength [τ = 2.42 as against 0.84 in *(1)*]. Treatment of the acid *(6)* with $LiAlH_4$ in tetrahydrofuran afforded the alcohol [b. p. 90—93 C/0.01 torr), which was oxidized and dehydrated by manganese dioxide in carbon tetrachloride to give *(7)* [b. p. 71—72 °C; NMR (CCl_4): AA'BB' system at τ = 3.3 and 4.1 and an AB system at τ = 7.60 and 9.10 with $J = -9.8$ Hz (cycloheptatriene protons)]. Reaction of *(7)* with *p*-toluenesulfonohydrazide in ethanol affords the tosylhydrazone *(8)* (m. p. 200—202 C, decomp.), which is subsequently heated in the presence of sodium methoxide in diethylene glycol diether to 100—120 C (1 h)[6].

Alkaline thermolysis of *(8)* yielded, instead of the expected cyclobutene hydrocarbon, the isomeric cage compound *(9)* [m. p. 168 C; NMR (CCl_4): multiplet at τ = 4.1 (2 olefinic H), AB system at τ = 9.19 and 9.50 with $J = 7.1$ Hz (2 cyclopropane H), and a multiplet at τ = 7.2—7.9 and 8.7—9.1 (10 aliphatic H)]. *(9)* is, however, none other than the product of a sterically favored intramolecular Diels-Alder reaction of the initial cyclobutene hydrocarbon—reacting in the norcaradiene form. Gas-phase pyrolysis of *(9)* at 400 C (in vacuum) results in both a retro-Diels-Alder reaction as well as a cyclobutene-butadiene isomerization of the regenerated cyclobutene hydrocarbon taking place with immediate formation of 7,12-dihydro-1,6-methano[12]annulene *(10)*, a light-sensitive liquid (b. p. 62—63 °C/0.02 torr), in 66% yield. On reaction with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ), *(10)* was dehydrogenated to the desired 1,6-methano[12]annulene, which could be isolated by chromatography on silica gel as a relatively stable orange-red compound (yield 36%; needles having m. p. 30—31 C after recrystallization from methanol).

The ^1H-NMR spectrum (CCl_4, 60 MHz) of 1,6-methano[12]annulene, which is not significantly temperature-dependent, shows an AA'BB' system with $\tau_A = 3.83$ (3-H, 4-H) and $\tau_B = 4.27$ (2-H, 5-H)[7] and a narrow multiplet at τ = 4.5 (7-H to 12-H) for the annulene protons, and an AB system at τ = 7.71 (13-H_a) and 3.00 (13-H_b) with $J = -11.51$ Hz for



the two bridge protons. Analysis of the AA'BB' system yielded values for the coupling constants of 2-H to 5-H ($J_{2,3}=5.5$ Hz, $J_{3,4}=10.8$ Hz, $J_{2,4}=0.33$ Hz, $J_{2,5}=1.2$ Hz), which clearly indicate the presence of a cycloheptatriene partial structure[8]. Hence the hydrocarbon must be present almost exclusively as the valence tautomer *(1)*.

The existence in *(1)* of a paramagnetic ring current, which is less obvious than in the isomeric 1,7-methano[12]annulene, is evident if the resonance conditions in *(1)* are compared with those in 9,10-dihydro-1,6-methano[12]annulene *(11)*[9]. According to Table 1 the transition from *(11)* to *(1)* affects the resonances of the protons of the cycloheptatriene moiety such that the AA'BB' system of 2-H to 5-H is shifted about 0.5 ppm upfield, while the doublets of 13-H_a and 13-H_b shift about 0.72 and 3.87 ppm, respectively, downfield.

The observed shifts of the signals can hardly be interpreted in any other way than by *(1)* displaying a paramagnetic ring current, in spite of the relatively strong deviation of the annulene ring from planarity. The remarkable finding that the resonances of the two bridge protons 13-H_a and 13-H_b appear at such different field strengths, would imply that *(3)* is the preferred conformation of the molecule. Model considerations show that the average distance from 13-H_b to the peripheral annulene ring in *(3)*—unlike in *(4)*—is noticeably smaller than that from 13-H_a, and it would be expected, therefore, that the paramagnetic ring current in *(3)* has more influence on 13-H_b than on 13-H_a. An X-ray structural analysis is to be carried out on the hydrocarbon in an attempt to confirm this tentative statement.

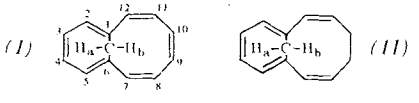


Table 1. Chemical shifts (τ values in CCl_4) of the protons of the cycloheptatriene moieties in *(1)* and *(11)*.

	τ 3-H, 4-H	τ 2-H, 5-H	τ 13-H_a	τ 13-H_b
(1)	3.83	4.27	7.71	3.00
(11)	3.30	3.70	8.43	6.87

The UV spectrum of *(1)* [λ_{max} (cyclohexane) = 254 (ε = 45900), 262 (46100), 337 (1400), 420 (440 sh), 296 nm (820)] resembles the UV spectra of the dehydro[12]annulenes[10] less than does that of 1,7-methano[12]annulene. This could be due to the considerable steric hindrance of the conjugation in *(1)*.

Received: December 28, 1973 [Z 975b IE]
German version: Angew. Chem. *86*, 231 (1974)

[1] For the synthesis of 1,7-methano[12]annulene see *E. Vogel, H. Königshofen, K. Müllen*, and *J. F. M. Oth*, Angew. Chem. *86*, 229 (1974); Angew. Chem. internat. Edit. *13*, 281 (1974).

[2] For definition of the term "isodynamic" see *J. F. M. Oth*, Pure Appl. Chem. *25*, 573 (1971).

[3] *J. A. Pople* and *K. G. Untch*, J. Amer. Chem. Soc. *88*, 4811 (1966).

[4] *E. Vogel* and *H. D. Roth*, Angew. Chem. *76*, 145 (1964); Angew. Chem. internat. Edit. *3*, 228 (1964).

[5] The yield of *(1)* can be almost doubled if the adduct mixture is used directly for further reaction and a separation carried out only after *(7)* has been formed.

[6] For the preparation of cyclobutenes by thermolysis of the tosylhydrazones of cyclopropanecarbaldehydes in basic medium see *J. A. Smith, H. Shechter, J. Bayless*, and *J. Friedman*, J. Amer. Chem. Soc. *87*, 659 (1965); *W. Kirmse* and *K.-H. Pook*, Chem. Ber. *98*, 4022 (1965).

[7] The assignment is based on the knowledge that the annulene protons 2-H, 5-H in 1,6-methano[10]annulenes engage in stronger long-range coupling with the *anti* than with the *syn* bridge protons.

[8] *H. Günther* and *H. H. Hinrichs*, Tetrahedron Lett. *1966*, 787.

[9] Unpublished work in collaboration with *H. Düwel*.

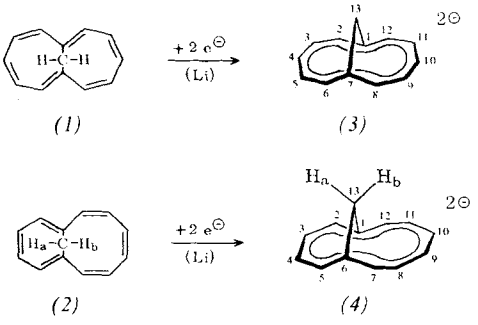
[10] *K. G. Untch* and *D. C. Wysocki*, J. Amer. Chem. Soc. *88*, 2608 (1966); *F. Sondheimer, R. Wolovsky, P. J. Garratt*, and *I. C. Calder*, *ibid. 88*, 2610 (1966).

The Dianions of 1,7- and 1,6-Methano[12]annulenes—Novel Aromatic 14π Electron Systems

By *Jean F. M. Oth, Klaus Müllen, Heinrich Königshofen, Max Mann, Yoshiteru Sakata*, and *Emanuel Vogel*[*]

NMR analysis has shown the presence of localized π bonds in the 4nπ electron systems 1,7-methano[12]annulene *(1)*[1] and 1,6-methano[12]annulene *(2)*[2]. In contrast to *(1)* and *(2)*, their dianions *(3)* and *(4)* represent (4n+2)π electron systems and should therefore exhibit aromatic character analogous to the dianions of [8]-, [12]-, and [16]-annulenes[3]. As is shown in the following, the properties of *(3)* and *(4)* are exactly as would be expected.

The polarographic reduction of the bridged [12]annulenes *(1)* and *(2)* (dropping-mercury electrode, 10^{-3} M solutions



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[**] *J. F. M. Oth* and *K. Müllen* thank the Schweizerischer Nationalfonds and Ciba-Geigy, Hoffmann-La Roche, Lonza, and Sandoz for their generous support.

in dimethylformamide, conducting salt tetra-*n*-butylammonium perchlorate) shows that both hydrocarbons undergo reversible transformation into their radical anions and dianions at relatively low potentials (see Table 1). Although

Table 1. Halfwave potentials for the reduction of *(1)* and *(2)* (relative to the standard calomel electrode). The reversibility of all reduction processes was demonstrated by cyclic voltammetry.

	$R + e^{\ominus} \rightleftarrows R^{\cdot\ominus}$	$R^{\cdot\ominus} + e^{\ominus} \rightleftarrows R^{2\ominus}$
(1)	−1.47 V	−1.79 V
(2)	−1.51 V	−1.72 V

the first and second reduction steps in *(1)* and *(2)* differ by only about 0.3 and 0.2 V respectively, it proved possible to electrochemically generate either the radical anions or dianions cleanly in a flow cell. In the case of the radical anion of *(1)*, an analysis of its ESR spectrum[4] showed the species to have C_{2v} symmetry. Hence, this radical anion, like those of other [4*n*]annulenes[5, 6], exhibits delocalized π bonding.

On the basis of the observed reduction potentials of *(1)* and *(2)* it was to be expected that both [12]annulenes can also be reduced with alkali metals to give the dianions *(3)* and *(4)* respectively. This in fact was found to be the case. *(3)* and *(4)* can easily be obtained—free from radical anions—by treating the corresponding hydrocarbon with lithium or potassium in 0.02 M D_8-tetrahydrofuran solution at −80 °C. Both the lithium salts and the potassium salts of *(3)* and *(4)* are completely stable at room temperature (in tetrahydrofuran).

The aromatic nature of the dianions *(3)* and *(4)* follows compellingly from a comparison of their ^{1}H-NMR spectra with those of *(1)* and *(2)*. As can be seen in Table 2, the transition from *(1)* and *(2)* to *(3)* and *(4)* is accompanied by a downfield shift of about 1—2 ppm of the annulene proton resonances, while the bridge protons are shifted 10—12 ppm or more upfield. These shifts may be regarded as proof of the existence of a diamagnetic ring current in *(3)* and *(4)*, as shifts of the same order of magnitude and direction have also been established in the formation of dianions of unbridged [4*n*]annulenes[7]. The fact that the resonances of the annulene protons 3-H, 4-H appear—unlike those in [12]annulene—at higher field strength than the resonances of the protons 2-H, 5-H[8], may likewise be regarded as a manifestation of the ring current effect. Interestingly, the noticeable difference in the chemical shifts of the bridge protons (4.7 ppm) in the [12]annulene *(2)*, which was recently attributed to bending of the peripheral annulene ring and the resulting difference in the mean distance of these protons from the ring, is almost absent in the dianion. Accordingly, in *(4)* the contribution of each of the bridge protons to the ring current effect are comparable; this would appear to be compatible only with the assumption that the ring is now strongly flattened[9]. This concept is further supported by the remarkable similarity in the resonance of *(3)* and *(4)*. The conversion of *(1)* and *(2)* into the dianions results, not only in changes in the chemical shifts, but also in extensive equalization of the originally strongly alternating vicinal coupling constants. That the occurrence of a rapid π-bond shift in the dianions can be ruled out on the basis of the temperature independence of their NMR spectra indicates that the C—C bonds of the annulene ring have experienced an adjustment in bond orders[10].

Supporting evidence for the aromatic structure of the dianions *(3)* and *(4)* deduced from comparative ^{1}H-NMR spectroscopy has also been provided by ^{13}C-NMR investigations.

Table 2. ^{1}H chemical shifts (τ values) and H,H coupling constants *J* (in Hz) of *(1)* and *(2)* and their dianions *(3)* and *(4)*. The spectra of *(3)* and *(4)* were recorded in D_8-tetrahydrofuran, the high-field signal of tetrahydrofuran (τ = 8.29) serving as standard.

	τ 2-H	τ 6-H	τ 3-H	τ 5-H	τ 4-H	τ 13-H	$J_{2,3}$	$J_{5,6}$	$J_{3,4}$	$J_{4,5}$
(1) at −135 °C	4.53	4.39	4.80	4.82	4.88	4.02	5.3	12.5	12.2	6.0
(1) at + 25 °C	4.46		4.81		4.88	3.96	9.0		9.2	
(3) at − 80 °C	2.84		3.72		3.59	16.44	8.4		10.7	

	τ2-H = τ5-H	τ3-H = τ4-H	τ7-H = τ12-H	τ 13-H_a	τ 13-H_b	$J_{2,3} = J_{4,5}$	$J_{3,4}$	$J_{2,13b}$
(2) at +25 °C	4.27	3.83	≈4.5	7.71	3.00	5.5	10.8	1.26
(4) at −80 °C	2.44	3.49		15.52	16.08	8.3	8.5	

In the case of *(3)* the ^{13}C-NMR spectrum shows only four signals[11] for the annulene protons; hence, it may be concluded—once again in combination with the temperature independence of the spectrum—that the molecule has C_{2v} symmetry.

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[1] *E. Vogel, H. Königshofen, K. Müllen*, and *J. F. M. Oth*, Angew. Chem. *86*, 229 (1974); Angew. Chem. internat. Edit. *13*, 281 (1974).

[2] *E. Vogel, M. Mann, Y. Sakata, K. Müllen*, and *J. F. M. Oth*, Angew. Chem. *86*, 231 (1974); Angew. Chem. internat. Edit. *13*, 283 (1974).

[3] *J. J. Katz*, J. Amer. Chem. Soc. *82*, 3784 (1960); *82*, 3785 (1960); *J. F. M. Oth* and *G. Schröder*, J. Chem. Soc. *B 1971*, 904.

[4] To be published.

[5] *J. F. M. Oth, H. Baumann, J.-M. Gilles*, and *G. Schröder*, J. Amer. Chem. Soc. *94*, 3498 (1972).

[6] *H. M. McConnell*, J. Chem. Phys. *28*, 107 (1958).

[7] Here, the inner annulene protons, insofar as they are available, are to be regarded as pendant to the bridge protons.

[8] This corresponds to the resonance in 1,6-methano[10]annulene: *H. Günther*, Z. Naturforsch. *20b*, 948 (1965).

[9] The flattening of the peripheral ring, which involves considerable strain, is indicative of a high resonance stabilization in *(4)*.

[10] *H. Günther* and *H. H. Hinrichs*, Tetrahedron Lett. *1966*, 787.

[11] In the transition from *(1)* to *(3)* the resonance of the bridge carbon atom shifts to high field by about the same amount as that of the bridge protons (10.5 ppm for C-13; 12.5 ppm for 13-H). Compounds *(1)* and *(3)* are therefore of interest in connection with the question of whether ring current effects are of importance in ^{13}C nuclear magnetic resonance.

Reviews

Abstracts of selected progress reports and review articles

Inositolphosphatide metabolism in externally stimulated cells is reviewed by *E. G. Lapetina* and *R. H. Mitchell*. The conversion of inositolphosphatides in many tissues is accelerated after addition of various types of compounds. The starting point of this stimulation is probably the cleavage of inositolphosphatides to diacylglycerols and cyclic inositol-1,2-phosphate or inositol-1-phosphate taking place on the cell surface. Resynthesis of the inositolphosphatide subsequently takes place within the cell. No biological function of this phenomenon has so far been reported; however, it is a regulation phenomenon independent of cyclic AMP. [Phosphatidylinositol Metabolism in Cells Receiving Extracellular Stimulation. FEBS Lett. *31*, 1—10 (1973); 94 references]

[Rd 678 IE—R]

Rearrangement reactions in organoboron chemistry have been classified in an article by *P. I. Paetzold* and *H. Grundke*. "Rearrangement" is defined here as the migration of a part of the molecule involving cleavage of a boron σ bond. The suggested classification differentiates rearrangements at tri-, tetra-, and higher-coordinated boron. The simplest example for the (3,1) shift at tricoordinated boron is the rearrangement of triallylborane:

$$(H_2C{=}CH{-}CH_2)_2BCH_2{-}CH{=}\overset{*}{C}H_2 \rightleftharpoons (H_2C{=}CH{-}CH_2)_2B{-}\overset{*}{C}H_2{-}CH{=}C$$

[Umlagerungen in der Organobor-Chemie. Synthesis 1973, 635—660; 169 references]

[Rd 690 IE—L]

Advances in the chemistry of Mannich bases is the subject of an article by *M. Tramontini*. Mannich aminomethylation reactions generally involve combined reaction of a substrate R—H (H = active hydrogen), formaldehyde, and a primary, or secondary amine. Not only can alkylketones, phenols, and

$$R{-}H + \underset{\underset{O}{\|}}{CH_2} + \underset{HN<}{} \xrightarrow[-H_2O]{} R{-}CH_2{-}N<$$

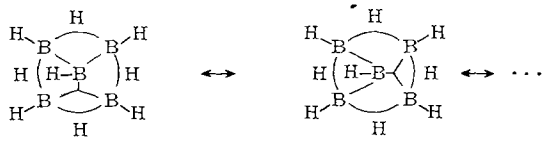
carboxylic acid derivatives be used as the substrate R—H, but also alkynes, heterocycles, and compounds that lead to N-, Se-, or P-Mannich bases of type

$>N{-}CH_2{-}N<$, $Alk{-}S{-}CH_2{-}N<$, $C_6H_5{-}Se{-}CH_2{-}N<$ and $>P(O){-}CH_2{-}N<$

The article provides a comprehensive overview of the advances made from 1960 through 1970. [Advances in the Chemistry of Mannich Bases. Synthesis 1973, 703—755; 461 references]

[Rd 691 IE—L]

The Chemistry of pentaborane(9) (B_5H_9) *(1)* is reviewed in an article by *D. F. Gaines*. The structure of the boron framework of *(1)* has almost the form of a square-based pyramid. Alkylations and halogenations and olefin addition occur exclusively at the apex position (B-1) in the presence of strong Lewis acids; nucleophilic conditions generally favor substitution at the equatorial (B-2) position, but side reactions often reduce yields. Strong Lewis acids react with B_5H_9 to form adducts having the general formula $B_5H_9 \cdot 2L$. Deprotonation



(1)

of B_5H_9, *e.g.* with alkylmetal hydrides gives rise to the anion $B_5H_8^-$; the proton is most likely removed from a bridging hydrogen position. The anion reacts with various group III, IV, and V compounds. [The chemistry of Pentaborane(9). Accounts Chem. Res. *6*, 416—421 (1973); 61 references]

[Rd 693 IE—L]

Patents

Abstracts of selected "Deutsche Offenlegungsschriften" (DOS), *i. e.* provisionally published specifications as filed with the German Patent Office

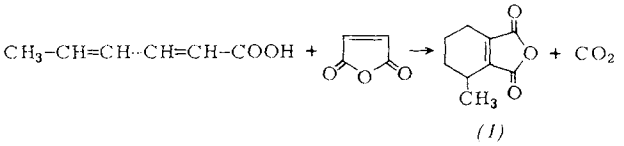
Oxalic acid and its esters are obtained by reaction of carbon monoxide with oxygen in an aqueous or alcoholic medium.

$$4\,CO + O_2 + 2\,H_2O \rightarrow 2\,(COOH)_2$$

The oxidation is preferably carried out in the pressure range 20—200 atm and with heating to at least 40 °C in the presence of a catalyst system that is soluble in the reaction medium and that consists of palladium chloride, copper(II) chloride, and lithium chloride. [DOS 2213435; Röhm GmbH, Darmstadt]

[PR 172 IE—D]

Isomer-free 3-methyl-3,4,5,6-tetrahydrophthalic anhydride *(1)* is obtained in a yield of about 68% by addition of sorbic acid to maleic anhydride in the temperature range 80—200 °C with simultaneous decarboxylation. *(1)* is liquid at room temperature, and can be used as a curing agent for epoxy

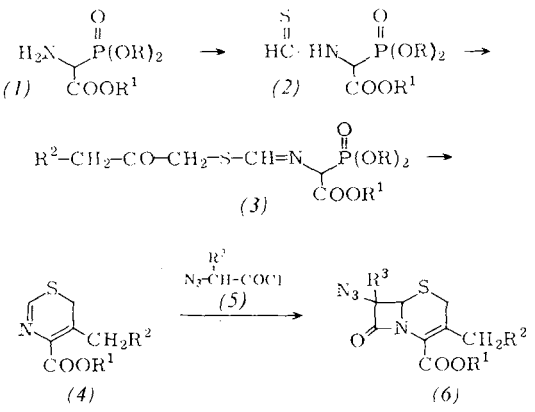


(1)

resins in solvent-free systems. [DOS 2315040; Ciba-Geigy AG, Basel (Switzerland)]

[PR 173 IE—D]

A new synthesis for cephalosporin intermediates *(6)* involves the condensation of the thiazinecarboxylic ester *(4)* with azidoacetyl chloride *(5)*; an interesting feature is the preparation

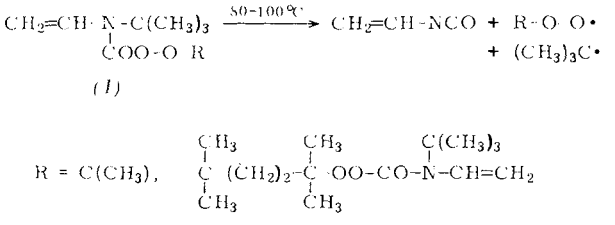


R^1 = protective group; R^2 = H, halogen, —O—CO—NH_2, alkoxy, aryloxy, —S—Het (Het = heterocyclic group), acyloxy, *etc.*; R^3 = H, CH_3, CH_3O

of *(4)* by an intramolecular Wittig-Horner reaction of *(3)*. [DOS 2318829; Merck & Co., Inc.; Rahway, N. J. (USA)]

[PR 174 IE—K]

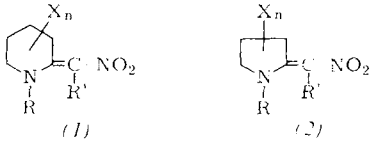
A new route to copolymers containing isocyanate groups starts with peroxycarbamic esters *(1)*, which are used as polymerization initiators. *(1)* decomposes in the course of the reaction



into vinyl isocyanate and free radicals. Polymers with high contents of built-in NCO groups have been obtained with ethylene as well as with styrene, butadiene, and ethyl acrylate. [DOS 2218365; Badische Anilin- & Soda-Fabrik, Ludwigshafen]

[PR 175 IE—A]

New groups of insecticidal substances having a novel mode of action are 2-nitromethylenepiperidines having the formula *(1)*, preferably obtained by reaction of 6-alkoxy-2,3,4,5-tetrahydropyridines or 2,2-dialkoxy-1-alkylpiperidines with nitroalkanes, and possibly substituted further, *e.g.* by halogenation, as well as corresponding pyrrolidine derivatives *(2)*.

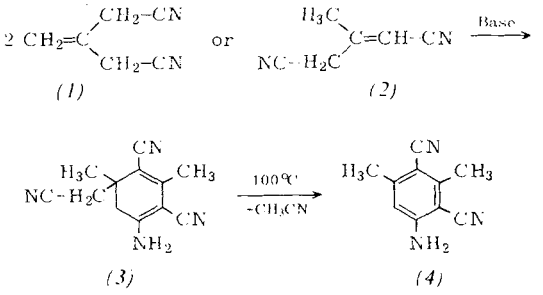


X = alkyl, aryl, OAlk, SAlk, Hal, *etc.*; R = H, alkyl, aryl, NO_2, acyl, *etc.*; R' = H, alkyl, aryl, NO_2, Hal, *etc.*

The compounds have a lethal action on some groups and stages of insects (caterpillars, beetles), while they reduce the mobility or coordination of others (*e.g.* flies). [DOS 2321552, 2321523; Shell International Research Mj., Den Haag (Netherlands)]

[PR 176 IE—S]

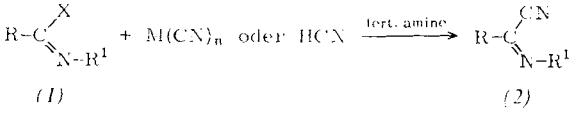
2,4-Dicyano-3,5-dimethylaniline *(4)* is obtained in good yields from β-methyleneglutaronitrile *(1)* or β-methylglutacononitrile *(2)* if the base-catalyzed dimerization of *(1)* or *(2)* is carried out above 100 °C. Under these conditions, the isolable cycliza-



tion product *(3)* undergoes aromatization with elimination of acetonitrile to form *(4)*. The compound *(4)* is a starting material for the preparation of azo dyes. [DOS 2222381; Bayer AG, Leverkusen]

[PR 177 IE—A]

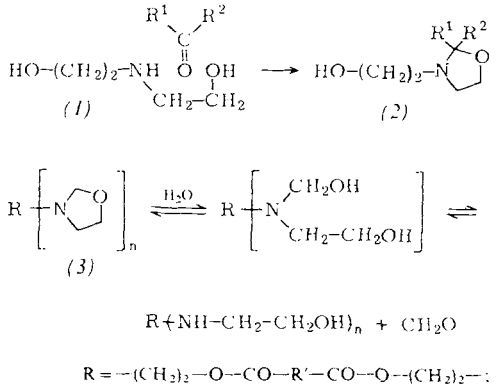
A new process for the preparation of α-imino nitriles *(2)* is based on the reaction of imidoyl halides *(1)* with metal cyanides or with hydrocyanic acid in the presence of a tertiary



amine (R, R^1 = alkyl, aryl, *etc.*; R^1 also: secondary amino, RO). [DOS 2221771; Bayer AG, Leverkusen]

[PR 184 IE—K]

Polyfunctional esters of *N*-hydroxyalkyloxazolidines of the type *(3)* give stable mixtures with polyisocyanates, which cure only on contact with atmospheric moisture. The compounds *(3)* are obtained by transesterification of hydroxyalkyloxazolidines *(2)* with esters of polybasic carboxylic acids such as dimethyl terephthalate or adipate. The compounds *(2)* are formed by the action of aldehydes or ketones on imino dialcohols *(1)*. The ring in *(3)* is cleaved by water. The polyiso-



R = —$(CH_2)_2$—O—CO—R'—CO—O—$(CH_2)_2$—; R' = —$(CH_2)_4$—, *p*-phenylene

cyanates react both with the hydroxy groups and with the amino group to form high polymers. Acrylic varnishes that cure in the presence of atmospheric moisture can be prepared from the methacrylic esters of *(2)* with isocyanates. [DOS 1952092, 1952001, 2018233; Rohm and Haas Company, Philadelphia (USA)].

[PR 185 IE—W]

Gesundheitsschädliche Arbeitsstoffe. Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten (Noxious Industrial Substances. Toxicological and Industrial Medical Grounds for MAC Values). Edited by *D. Henschler*. Verlag Chemie, Weinheim 1972. 1st ed., xiii, 220 pp., 1 figure and 50 tables. Loose-leaf DM 58.—.

This work presents clearly and impressively the brief information assembled by the Commission for the Testing of Noxious Industrial Substances of the Deutsche Forschungsgemeinschaft as a basis for the maximum allowable concentrations (MAC values) of individual noxious substances.

At the start of the discussion of the individual substances, the currently valid MAC values and the last date on which they were fixed are given; these are followed by the principal synonyms, chemical name, molecular and structural formulas, the main physical and chemical properties, and finally information on conversion from ppm to mg/m^3 and *vice versa*. Under the heading "General Action Character" the reader is informed about absorption, metabolism, excretion, and the main effects and modes of action. This is followed by the sections "Experience with Human Subjects", which includes the results of industrial toxicological, occupational medical, and feld investigations as well as descriptions of cases, "Results of Animal Experiments", which includes data on the acute and chronic effects on experimental animals, and finally a brief "Justification of the MAC Value". The arrangement facilitates a clear presentation of the facts and allows fast orientation and the correct toxicological appraisal of the substance.

Unfortunately, the work does not yet include important substances that are of very frequent occurrence and are therefore of great interest (*e.g.* xylene, toluene, and styrene). Moreover despite the understandably advocated view that no MAC values can be given for substances that are believed to cause cancer, one might wonder whether it would have been better to give guide values in the interests of controllability, since no control of these very dangerous emissions, such as benzene, is possible if no limiting value exists.

Finally, the ring-book form chosen allows the easy addition of further material and the replacement of pages as a result of revision.

Georg G. Fodor [NB 182 IE]

MTP International Review of Science. Theoretical Chemistry. Physical Chemistry, Series One. Vol. 1. Edited by *W. Byers Brown*. Butterworths, London University Park Press, Baltimore 1972. 1st ed., 295 pp., numerous figures and tables, bound £ 10.—.

The MTP review is an ambitious project aimed at presenting an encyclopedic survey, initially in 33 volumes, of research in chemistry for the years 1967—1971, with the addition of a new series every two years. The present volume on theoretical chemistry contains $4\frac{1}{2}$ contributions on quantum-chemical topics, $2\frac{1}{2}$ on areas of statistical thermodynamics, and a review on molecular scattering theory. This distribution fully corresponds to the current distribution of interest within theoretical chemistry. Each article contains exhaustive literature references (about 100 to about 450 per contribution), which are critically discussed in the text. This makes the volume a real mine of information.

The quantum-mechanical contributions deal with *ab-initio* calculations for atoms (*J. I. Musher*), for diatomic molecules (*A. C. Wahl*), and for organic molecules (*L. Radom* and *J. A. Pople*), for these last in the Hartree-Fock (or SCF) approximation and for atoms and diatomic molecules with inclusion of electron correlation. The article by *Musher* is rather individual. *Wahl* rightly points out the significance of the reliability that has now been achieved in quantum-chemical calculations to a close contact between experiment and theory. In the article on properties of molecules, *W. N. Lipscomb* discusses second-order properties such as electric polarizability, diamagnetic susceptibility, and chemical shift for diatomic molecules, calculated by the coupled Hartree-Fock method. Other properties of molecules are discussed by *Wahl* and by *Radom* and *Pople*. The articles on statistical thermodynamics deal mainly with liquids, and specifically with their equilibrium theory (*D. D. Fitts*) and the theory of transport processes (*A. R. Allnatt* and *L. A. Rowley*). The importance of computer simulation (molecular dynamics and Monte Carlo method) in present-day research is made particularly clear in the article by *Fitts*.

The theory of intermolecular forces, which is dealt with by *P. R. Certain* and *L. W. Bruch*, comes from quantum chemistry, but affects mainly the statistical theory. Equal consideration is given to both aspects.

The article by *R. D. Levine* on the theory of molecular collisions critically examines in particular the conditions under which the methods suggested (classical and quantum-mechanical) are good and practicable approximations.

On the whole, the author and his team of experts must be congratulated on this survey of recent developments in theoretical chemistry.

Werner Kutzelnigg [NB 185 IE]

Die Woodward-Hoffmann-Regeln und ihre Anwendung [The Woodward-Hoffmann Rules and their Use]. By *N. T. Anh*. Translated and edited by *H.-J. Hansen* and *H. Heimgartner*. Verlag Chemie GmbH, Weinheim/Bergstr. 1972. 1st ed., xiv, 254 pp., 87 figs., 2 tables, bound DM 28.—.

Following the monograph "Die Erhaltung der Orbitalsymmetrie" [The Conservation of Orbital Symmetry] by *Woodward* and *Hoffmann* (1970), another work on this subject is now available; it is a German translation of "Les règles de Woodward-Hoffmann" [The Woodward-Hoffmann Rules] by *N. T. Anh*, which was published in 1970.

The book begins with an introduction (16 pp.) to the elementary concepts of the MO theory, insofar as these are necessary for an understanding of the Woodward-Hoffmann rules. In the main part (165 pp.), the theory of concerted reactions according to the definition given by *Woodward* and *Hoffmann* (electrocyclic, sigmatropic, *etc.*) is first derived and then discussed in detail in separate chapters with the aid of reactions that have actually been observed. The concepts of *Dewar*, *Fukui*, and *Zimmermann* are then briefly presented and the possible application of the rules to several reactions (metal-ion catalysis, photochemistry, *etc.*) is discussed in two sections (49 pp.). An author and subject index completes the book.

The author's aim of appealing both to advanced students and to organic chemists engaged in research is achieved on the one hand by the inclusion of many problems for practice in the text and on the other by the provision of a comprehensive survey of the literature (up to March 1971) for each chapter. In the reviewer's opinion, this includes all the most important contributions on this topic.

Clear drawings, clear language, and the division into "theoretical" and "practical" sections enable even the newcomer to

[1] Cf. Angew. Chem. 6, 1009 (1967).

gain a grounding in this field without any special prior knowledge. For the advanced reader, however, it would have been better if the author of this otherwise very commendable book had taken a more critical attitude with regard to the theory and particularly to the experimental results.

Eckhart Schmidt [NB 191 IE]

Aufschlussmethoden der anorganischen und organischen Chemie [Digestion Methods in Inorganic and Organic Chemistry]. By *R. Bock*. Verlag Chemie GmbH, Weinheim/Bergstr. 1972. 1st ed., 232 pp., 46 figs., 75 tables; bound DM 64.—.

The conversion of samples into a form that is amenable to chemical or physical methods of analysis is achieved by the use of suitable procedures for sample preparation. For example, solid samples that are insoluble in acids or alkalis can be digested by melting; the phosphorus or boron contents of organic substances can be determined after digestion by oxidative methods, and the sulfur content can be determined by combustion of these substances or of gaseous samples, followed by absorption of the combustion gases in alkaline liquids. The author has managed to present a self-contained treatment of the diverse methods of sample preparation and to indicate their sources of error, which affect the correctness of the overall result of an analysis as much as the subsequent quantitative determination, but which, like sampling, frequently do not receive the required care and attention.

The monograph has been systematically and carefully built up, with reference to about 1600 widely scattered publications, which are often difficult to find. The first section deals with general aspects of digestion methods, the digestion procedures, suitable apparatus materials, sources of error and loss of substance, and finally the use of blanks. The purely physical dissolution of inorganic and organic substances is discussed in the second section, and digestion by the use of heat, electrical energy, and UV and γ radiation, *i.e.* degradation methods using pyrolysis, spark discharge, electron bombardment, or photoionization, is described in the third section. The fourth section deals with general methods for digestion by means of chemical reactions, *e.g.* with complexing agents or acids, and fusion with neutral, acidic, or basic salts. Finally, the fifth and sixth chapters are concerned with digestion methods involving oxidation or reduction processes.

This commendable book should find a place in any analytical laboratory. It will provide many inorganic and organic chemists with suggestions for chemical and physical investigations on their samples. It will also be useful in purity checks and trace analyses on technical products.

Hermann Kienitz [NB 192 IE]

Magnetic Resonance. Oxford Chemistry Series. By *K. A. McLauchlan*. Clarendon Press, Oxford 1972. 1st ed., xii, 105 pp., numerous figures, bound £ 1.20.

The independence of chemical research in the field of free radicals on the one hand and of diamagnetic substances on the other has its counterpart, among physical methods, in the division that is made in research, and in theory in general, between electron spin spectroscopy and nuclear spin spectroscopy. It is therefore gratifying that a renewed effort is made here to bring ESR and NMR spectroscopy together under the broader heading of "Magnetic Resonance". In this way it is possible to show the many points in common in the physical principles and in the experimental techniques, and also the characteristic differences between the two methods.

In the space of about 100 pages the author presents the important aspects of magnetic resonance [chapter headings (number of pages): The Principles (20); Spectra from Liquids (12); The g-Factor (10); The Chemical Shift (16); Interactions between Magnetic Particles (12); Analysis of Spectra (12); The Solid State (14)]. However, he is forced to forgo detailed derivations in the formulation of quantitative relationships. The book therefore calls for a good grounding in physics in general, and quantum mechanics in particular. It is mainly suitable for physicists and physical chemists. Advanced students of inorganic and organic chemistry may use it as a guide if they are prepared to work through the material with the aid of more detailed textbooks.

Harald Günther [NB 194 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal.

Comparative Physical Biology. By *N. R. Joseph*. S. Karger Basel 1973. VII, 234 pp., bound DM 83.—.

Contents: Internal Environment; Protoplasm; Electromotive Force; Colligative Properties; Skeletal Muscle; The Heart; Growth and Development; Energy and Entropy; Heterogeneous Equilibrium; Metabolic Energy; Sets and Monograms.

Annual Reports in Organic Synthesis—1972. Edited by *J. McMurry* and *R. B. Miller*. Academic Press, New York 1973. xii, 273 pp., stitched $ 7.40.

Contents: Carbon-Carbon Bonds; Oxidations; Reductions; Heterocycles; Protecting Groups.

Magnetic Resonance and Related Phenomena. Edited by *V. Hovi*. North-Holland Publishing Company, Amsterdam 1973. xxxiv, 555 pp., bound Dfl. 120.00.— Proceedings of the XVIIth Congress, Ampere Turku, August 1972.

Biochemie antimikrobieller Wirkstoffe. By *T. J. Franklin* and *G. A. Snow*. Translated and edited by *W. Goebel*. Vol. 116 of the Series "Heidelberger Taschenbücher". Springer Verlag, Berlin 1973. xii, 183 Vol. 116 of the Series DM 16.80.

Chemistry. Imagination and Implication. By *A. T. Schwartz*. Academic Press, New York—London 1973. xv, 571 pp., bound $ 10.95.

Electron Spin Resonance, Vol. 1. Edited by *R. O. C. Norman*. The Chemical Society London 1973. x, 273 pp., bound £ 7.00.—A volume in the series "Specialist Periodical Reports".

Electron Deficient Compounds. By *K. Wade*. From the series "Studies in Modern Chemistry". Nelson, London 1973. vi, 203 pp., stitched £ 1.95.

Contents: Diborane; Higher Boranes and Boron Polyhedra; Boron Hydrides; Metal Hydrides, Alkyls, and Aryls; Carboranes.

Methoden zur Optimierung chemischer Reaktoren. By *G. M. Ostrowski* and *J. M. Wolin*. Akademie-Verlag, Berlin 1973. xvii, 244 pp., bound DM 68.—.

Modern Aspects of Inorganic Chemistry. By *J. J. Emeleus* und *A. G. Sharpe*. Routledge and Kegan Paul, London 1973. xi, 677 pp., bound £ 5.25.

Liquid Crystals. Edited by *F. C. Tompkins*. Symposia of The Faraday Society No. 5, 1971. The Faraday Division, Chemical Society, London 1973. 188 pp., stitched £ 4.00.

Molecular Motions in Amorphous Solids and Liquids. Edited by *F. C. Tompkins*. Symposia of The Faraday Society No. 6, 1972. The Faraday Division, Chemical Society, London 1973. 197 pp., stitched £ 4.00.

Gmelins Handbuch der anorganischen Chemie. Supplement to 8th Edit. Vol. 5: Kobalt-organische Verbindungen, Part I: Einkernige Verbindungen. Verlag Chemie- Weinheim 1973. viii, xii, 527 pp., bound DM 696.—.

Gmelins Handbuch der anorganischen Chemie. Supplement to 8th Edit. Vol. 6: Kobalt-organische Verbindungen, Part II: Mehrkernige Verbindungen. Verlag Chemie, Weinheim 1972. vi, vi, 243 pp., bound DM 329.—.

Das Leben und Wirken von Hans Fischer. By *A. Treibs*. Hans-Fischer-Gesellschaft, München 1973. 681 pp., bound.

Gmelins Handbuch der anorganischen Chemie. System No. 61: Silber. Part B 3: Verbindungen mit Schwefel, Selen, Tellur, Polonium, Bor, Kohlenstoff und Silicium. Verlag Chemie, Weinheim 1973. vi, xx, 389 pp., bound DM 531.—

Physical Chemistry Series One. Index Volume. Edited by *A. D. Buckingham*. From the series "MTP International Review of Science". Butterworths, London/University Park Press, Baltimore 1973. ix, 284 pp., bound £ 5.00.

Gmelins Handbuch der anorganischen Chemie. System No. 39: Seltenerdelemente. Part A 2: Scandium. Geschichtliches, Vorkommen. Verlag Chemie, Weinheim 1973. vi, vi, 181 pp., bound DM 254.—.

The Organic Chemist's Book of Orbitals. By *W. L. Jorgensen* and *L. Salem*. Academic Press, New York—London 1973. xii, 305 pp., bound $ 11.50.

Contents: How Molecular Orbitals Are Built by Delocalization: A Unified Approach Based on Bond Orbitals and Group Orbitals; Basic Data Concerning Orbital Drawings; Three-Dimensional Molecular Orbitals.

Gmelins Handbuch der anorganischen Chemie. System No. 48, 49, 50: Vanadium, Niob, Tantal. Verlag Chemie, Weinheim 1973. vi, 352 pp., bound DM 456.—.

Reaktionsmechanismen der Organischen Chemie. Ein Seminarbuch. By *H. Höver*. Verlag Chemie, Weinheim/John Wiley and Sons, Frankfurt 1973. 565 pp., stitched DM 48.—

Contents: Additionsreaktionen; Valenzisomerisierungen, Eliminierungen; Fragmentierungen; Substitutionen; Radikal-Reaktionen; Photochemie.

Organic Syntheses, Collected Volume 5. A Revised Edition of Annual Volumes 40—49. Edited by *H. E. Baumgarten*. John Wiley and Sons, New York 1973. xiv, 1234 pp., bound £ 13.00.

The Alkaloids, Vol. XIV. Edited by *R. H. F. Manske*. Academic Press, New York 1973. xvii, 610 pp., bound $ 42.50.

An Introduction to Mathematical Organic Chemistry. By *J. E. Banfield*. Gereng, Armidale 1972. xiii, 690 pp., bound.

Kunststoffe III. Spritzgießen, Extrudieren, Blasformen. By *H. Domininghaus*. VDI-Taschenbücher, T. 48. VDI-Verlag, Düsseldorf 1973. x, 194 pp., stitched DM 22.80.

Nitrogen NMR. Edited by *M. Witanowski* and *G. A. Webb*. Plenum Press, London 1973. ix, 403 pp., bound $ 32.00.

Contents: Theoretical Background; Experimental Aspects; ^{14}N Nuclear Quadrupole Effects; Chemical Shifts; Coupling Constants.

Methoden zur Orientierung komplexer verfahrenstechnischer Systeme. By *G. M. Ostrowski* and *J. M. Wolin*. Akademie-Verlag, Berlin 1973. xii, 331 pp., bound DM 86.—.

Hagers Handbuch der Pharmazeutischen Praxis. Für Apotheker, Arzneimittelhersteller, Ärzte und Medizinalbeamte. Edited by *P. H. List* and *L. Hörhammer*. Vol. 4: Chemikalien und Drogen (CI—G). Springer-Verlag, Berlin 1973. 4., completely revised, xii, 1226 pp., bound DM 236.—. Subject index to Vols. 1, 2, 3, 7A: iv, 240 pp., stitched DM 38.—.

Massenspektrensammlung von Lösungsmitteln, Verunreinigungen, Säulenbelegmaterialien und einfachen aliphatischen Verbindungen. By *M.* and *G. Spiteller*. Springer, Wien—New York 1973. xv, 62 pp., bound DM 58.—.

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Oxidative Coupling *via* Organocopper Compounds[1]

By Thomas Kauffmann[*]

Dedicated to Professor Heinrich Hellmann on the occasion of his 60th birthday

The type of reaction described here, which achieved preparative importance before the turn of the century in the form of the Glaser reaction, has found new applications in recent years: syntheses of 1,3-dienes, 2,3,6,7-tetraaza-1,3,5,7-tetraenes, 2,3-diaza-1,3-dienes, hydrazine derivatives, bis(heteroallyl) compounds, hetarenes, polyhetarenes, cyclopolyarenes, protophanes, phanes, and heteraprotophanes. The reaction, which consists in the metalation of the starting substance followed by oxidative coupling of the metal derivative, merits special preparative interest when several successive coupling processes are possible (*e. g.* polyyne, polyarene, cyclopolyarene, and protophane syntheses). The main factors limiting its applicability are the high thermal stability of some organic copper compounds and the disproportionation of the ligands that frequently occurs as a competing reaction. Selective asymmetric linkages are not generally possible by this method.

1. Introduction

Table 1 presents a list of reactions discovered before 1920 in which organocopper compounds or copper cyanide play an important role.

The reactions listed in Table 2 are of the same type, but these were discovered within the last decade, and reflect a reawakening of interest in organocopper chemistry. The most significant advance seems to lie in the use of cuprate complexes. The thermal stability of organocopper compounds is enhanced in these complexes, and this favors reactions with organic halides (substitution), and unsaturated compounds (addition). Moreover, the organic residues are spatially proximate in cuprate complexes, so that oxidative couplings may be promoted.

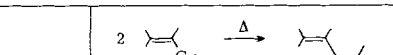
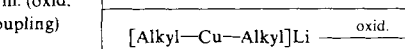
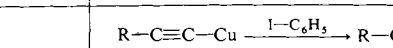
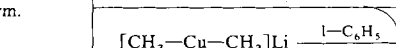
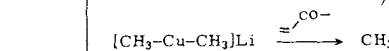
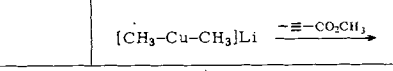
Table 1. Reactions from early organocopper chemistry.

Substitution	sym. (oxidative coupling)	$2R{-}C{\equiv}C{-}Cu \xrightarrow{oxid.} R{-}C{\equiv}C{-}C{\equiv}C{-}R$	Glaser reaction [2]	1869
		$2N{\equiv}C{-}Cu \xrightarrow{oxid.} N{\equiv}C{-}C{\equiv}N$	*Jaquemin* [3]	1885
		$2Ar{-}Hal \xrightarrow{Cu} Ar{-}Ar$	Ullmann biaryl synthesis [2, 17]	1904
	asym.	$N{\equiv}C{-}Cu \xrightarrow{Hal-Ar} N{\equiv}C{-}Ar$	Rosenmund/ von Braun nitrile synthesis [2]	1919
		$N{\equiv}C{-}Cu \xrightarrow{N_2^{\oplus}-Ar} N{\equiv}C{-}Ar$	Gattermann nitrile synthesis [2]	1880
Addition		$R{-}C{\equiv}C{-}Cu \xrightarrow{HC{\equiv}C-R'} R{-}C{\equiv}C{-}CH{=}CH{-}R'$	Straus reaction [4]	1905

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This work was supported by the Deutsche Forschungsgemeinschaft, the Landesamt für Forschung des Landes Nordrhein-Westfalen, and the Fonds der Chemischen Industrie.

Table 2. Reactions from more recent organocopper chemistry.

Substitution	sym. (oxid. coupling)		[5, 6]	1966
			[7]	1967
	asym.		[8]	1966
			[9]	1967
Addition			[10]	1966
			[11]	1969

We have systematically investigated oxidative coupling *via* organocopper compounds, concentrating on the *exploration of the unusually wide range of applications rather than on the study of the mechanism.* It was possible to exclude the linkage of sp-hybridized C atoms, which has already been extensively studied; the linkage of N atoms was included.

2. Fundamental Aspects

The oxidative coupling of organic compounds *via* metal derivatives as shown in eq. (1), is a symmetrical *substitution with metalation/ligand coupling mechanism*[20]. A characteristic feature is that the two residues to be linked are both bonded to metal at some stage. Though this type of reaction has been known for some time, and is not without importance in preparative work, it has not yet found a secure place in the classification of organic reactions. The occasional reference in textbooks under the heading of free radicals[12] seems unsatisfactory, since free radicals mostly cannot be detected in these reactions[12].

$$\underset{X=H,\,Hal}{R{-}X} \xrightarrow{\text{metalation [20]}} [R-M] \xrightarrow[\text{coupling}]{\text{ligand}} \tfrac{1}{2}R{-}R + M \qquad (1)$$

Numerous metals, particularly transition metals, are suitable for couplings in accordance with eq. (1); however, the reactions generally proceed especially smoothly on copper, and with surprising tolerance as far as the nature of the ligands is concerned. Hetero atoms such as N, P, and S can be linked as well as sp-, sp^2-, and sp^3-hybridized C atoms[13].

The *introduction of copper* into an organic compound can be achieved either directly (terminal alkynes, aryl halides, compounds with NH groups)[14] or *via* an intermediate containing some other metal (metalation-transmetalation route[20]; cf. *e.g.* Sections 3.1.2 and 3.2). The subsequent coupling of the ligands is *oxidative*; an added oxidizing agent may be reduced instead of the metal. An oxidizing agent is necessary if a Cu^I compound with an excessively high thermal stability is formed as an intermediate (cf. *e. g.* Section 3.1.4). The coupling of the ligands, which is represented only by the overall formulation in eq. (1), can proceed *monocentrically* [eq. (2)] or *dicentrically* (two one-electron transfers) [eq. (3)]. The dicentric reaction must take place in an organometallic aggregate, if one ignores the rare cases in which free radicals are involved (possibly at high temperatures).

$$\text{monocentric: } R{-}Cu^x{-}R \rightarrow R{-}R + Cu^{x-2} \qquad (2)$$

$$\text{dicentric: } Cu^x{-}R + Cu^x{-}R \rightarrow R{-}R + 2Cu^{x-1} \qquad (3)$$

A reaction whose mechanism has been particularly thoroughly studied is the coupling of *m*-trifluoromethylphenyl ligands bonded to Cu^I, which proceeds in the case of the octamer *(1)* in benzene at 74 °C. Since a stable Cu^0—Cu^I cluster *(2)* is formed *via* a labile Cu^0—Cu^I cluster[15], the coupling very probably proceeds dicentrically, as is also assumed in the Glaser reaction[16]. Free radicals cannot be detected in either reaction[15, 16].

$$\underset{(1)}{R_8Cu_8} \xrightarrow{k_1} R_2 + \underset{R = m\text{-}F_3C{-}C_6H_4}{R_6Cu_8} \xrightarrow{k_2} R_2 + \underset{(2)}{R_4Cu_8}$$

Oxidative couplings *via* organocopper compounds have been mainly used where suitable copper compounds are formed directly (Ullmann reaction[17]) and even in aqueous solution (Glaser reaction and variants, dicyanogen synthesis), and where the coupled residues can be readily modified by synthesis and degradation reactions, as in the case of dicyanogen, diacetylenes, and biaryls. A particularly interesting synthetic possibility is offered when the coupling product allows further couplings of the same type. This is generally so in the case of compounds of type *(3)* in which X can be replaced directly or indirectly with copper:

$$\underset{(3)}{X{-}R{-}X} \rightarrow X{-}R{-}R{-}X \rightarrow X{-}R{-}R{-}R{-}R{-}X \rightarrow \cdots\cdots \qquad X = H, Hal$$

Well-known examples of such multiple oxidative couplings are the syntheses of open-chain and cyclic polyynes[18]. (For further examples see Sections 3.2, 3.3, 3.4, 4.5.2, and 4.5.3.)

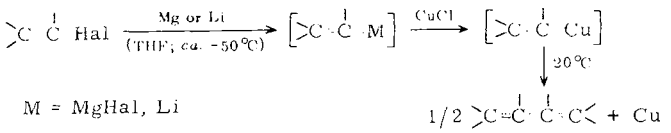
3. Linkages of C or N Atoms with sp^2 Hybridization

3.1. Synthesis of Open-Chain Conjugated Systems

3.1.1. 1,3-Dienes

After the discovery of the oxidative coupling of alkynes *via* organocopper compounds (Glaser reaction), almost a century passed before two research groups working independently applied the reaction to alkenes. Because of the low acidity of these compounds it was necessary to start with halides and to introduce the copper by the metalation/transmetalation route[5, 6, 19, 20] (Table 3).

On thermal decomposition of the stereoisomeric 1-propenylcopper and 2-butenylcopper compounds *(4a)* and *(4b)*, the coupling takes place with full retention. This stereospecificity makes the new 1,3-diene synthesis valuable for preparative



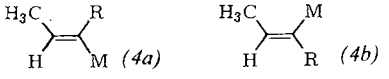
M = MgHal, Li

Table 3. Synthesis of 1,3-dienes from alkenyl halides. Metalation with magnesium (yields in brackets: with lithium); transmetalation with CuCl.

Alkenyl halide	Yield [%]	Ref.
CH_2=CH—Cl	81	[6, 22]
CH_3—CH=CH—Br [a]	74 [a]	[6, 22]
$(CH_3)_2$C=CH—Br	96	[6, 22]
trans-β-bromostyrene [b]	58 [c]	[6, 22]
1-Bromo-1-cyclopentene	22 (16)	[23]
1-Bromo-1-cyclopentene [b]	17	[23]
1-Bromo-1-cyclohexene	3.5 (5)	[23]
1-Bromo-1-cyclohexene [d]	3.5	[23]

[a] *cis-trans mixture.*
[b] The organocopper(I) compound was still stable at 60 C, and consequently had to be oxidized with oxygen.
[c] *trans,trans* compound.
[d] Transmetalation with $CuBr_2$.

use and practically rules out the occurrence of alkenyl radicals, since the 1-propenyl and 2-butenyl radicals may be expected to undergo very fast inversion of configuration[5].



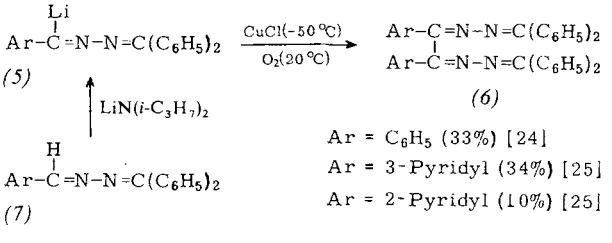
(4a) *(4b)*

R = H, CH_3; M = Cu^I, Cu^I←$P(C_4H_9)_3$

The alkenylcopper compounds required for the coupling have also been prepared by addition of alkylcopper compounds to alkynes[21].

3.1.2. 2,3,6,7-Tetraaza-1,3,5,7-tetraenes

Unlike in the alkenes, the H atom on the sp^2-C atom of the azines *(7)* is so acidic that it can readily be replaced by lithium. These azines have been coupled to form the tetraazatetraenes *(6)* by the successive action of lithium diisopropylamide and $CuCl/O_2$ in THF[24–26]. The lithium compound *(5)*, Ar = C_6H_5, (deep green solution) was detected by NMR spectroscopy of the deuterolysis product. However, only 6% of the compound *(7)* had been metalated at 0 °C.



(5) *(6)* *(7)*

Ar = C_6H_5 (33%) [24]
Ar = 3-Pyridyl (34%) [25]
Ar = 2-Pyridyl (10%) [25]

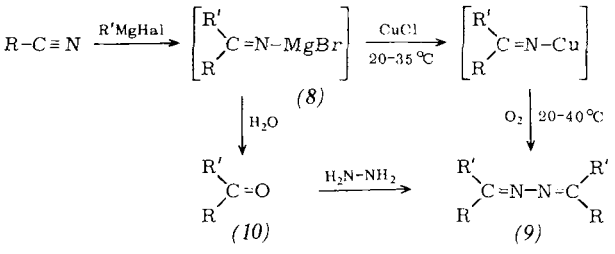
In the case of *(6)*, Ar = C_6H_5, hydrolysis with 30% H_2SO_4 led to the 1,2-diketone in a yield of 63%[25]. Since the azines *(7)* are prepared from aldehydes, the reaction allows 1,2-diketone syntheses

2 Ar—CH=O → Ar—CO—CO—Ar

in which =N—N=C(C_6H_5)$_2$ acts as a masking group.

3.1.3. 2,3-Diaza-1,3-dienes (Ketazines)

Substituted methyleneamidomagnesium halides *(8)*, which are readily obtainable by the action of Grignard compounds on nitriles, are converted by CuCl in THF/ether mixtures into thermally fairly stable copper(I) amides, which react rapidly with oxygen to form ketazines *(9)*. This ketazine synthesis is more elegant than the synthesis nitrile→ketone *(10)*→ketazine *(9)* in which the N atom is first eliminated from *(8)* as NH_3 and then reintroduced with hydrazine. Since the yields (Table 4) are practically the same as in ketone syntheses *via (8)*, it may be assumed that the transmetalation and coupling step proceeds almost quantitatively. The best yields are obtained with catalytic quantities of CuCl[27, 28].

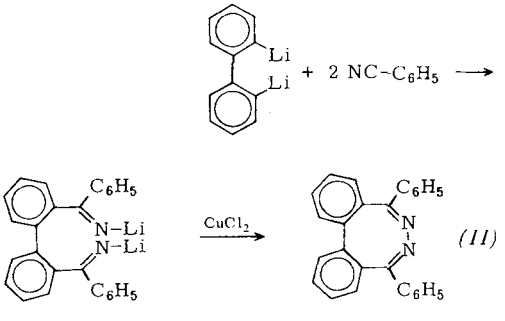


(8) *(10)* *(9)*

Table 4. Synthesis of ketazines *(9)* *via* substituted copper(I) *N*-methyleneamides in THF/ether (for descriptions of experiments and other analogous reactions see [28]).

R	R′	mol Cu / mol nitrile	Yield [%]
C_6H_5	C_6H_5	1	72
		0.3	86
		0.05	94
C_6H_5	*n*-C_4H_9	0.2	79
o-Br—C_6H_4	C_6H_5	0.1	89
p-Br—C_6H_4	C_6H_5	0.1	93
α-naphthyl	C_6H_5	0.1	70
α-naphthyl	α-naphthyl	0.1	64
α-naphthyl	C_2H_5	0.1	64
$(CH_3)_2$CH	C_6H_5	0.2	69
C_2H_5	C_6H_5	0.2	72
C_2H_5	*p*-CH_3—C_6H_4	0.2	76
C_2H_5	C_2H_5	0.2	40

Attempts to make use of the linkage of imino groups for cyclization have been successful in only one case. Despite the application of the dilution principle, the yield of 5,8-diphenyldibenzo[*d,f*][1,2]diazocine *(11)* was only 14%[29].

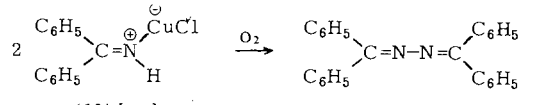


(11)

The yellow copper(I) amides RR′C=N—Cu with R = R′ = *p*-tolyl or phenyl have been isolated in an almost pure state from dioxane. The dry crystals are stable to air for a few hours at 20 °C; decomposition begins at 140 °C under nitrogen, and the compounds are quantitatively hydrolyzed to the

ketones by hot dilute hydrochloric acid. When oxygen is led into the THF solution, the ketazines *(9)* are formed (100 and 63 % respectively). A yield of 100 % makes the intermediate occurrence of free radicals extremely unlikely[29].

The CuCl-catalyzed oxidation of *free* diphenylmethanimine to the ketazine (92%) at 120 °C/6 atm of O_2 is described in a patent[30]. In our experience the reaction also proceeds in benzene at 20 °C/1 atm of O_2 (40 %)[29]. The intermediate *(12)* containing copper[31] was isolated in the form of colorless crystals (m. p. 132 °C; 82 %) when the reaction was carried out with an excess of CuCl *under nitrogen*. Solid *(12)* is stable in air, but when dissolved in benzene it is rapidly oxidized to the ketazine[29].



(12) [20] 72%

Since substituted methyleneamidomagnesium halides of the type *(8)* are generally more easily obtainable than the free ketimines, which are often unstable, the coupling of the magnesium compounds is likely to be of greater practical importance than that of the free compounds.

3.1.4. Dialkylamino-Substituted 2,3-Diaza-1,3-dienes

N'N'-Dialkyl-substituted amidines *(14)* have also been coupled in preparatively useful yields (Table 5)[32]; the metalated amidines *(13)* (M = Li, MgBr) were prepared by the route indicated (yield 80—100%)[33].

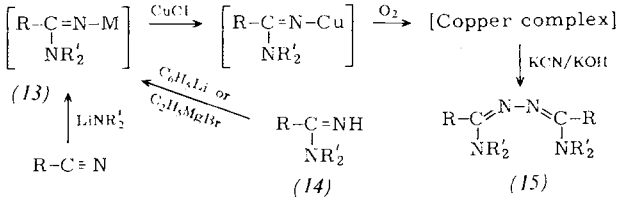


Table 5. Synthesis of 2,3-diaza-1,3-dienes of the type *(15)* from N^1,N^1-dialkylated metalated amidines *(13)* in 1,2-dimethoxyethane/ether mixtures at 85 °C, coupling with $CuCl/O_2$ (yields in brackets: with $CuBr_2$) [32, 33].

R	2 R'	M	Yield [%]
C_6H_5	$-(CH_2)_5-$	Li	74 (71)
C_6H_5	$-(CH_2)_5-$	Li	18 [a]
C_6H_5	$-(CH_2)_4-$	Li	69
C_6H_5	$-(CH_2)_2-O-(CH_2)_2-$	Li	83
C_6H_5	$-CH_3$ CH_3-	Li	67 (69)
C_6H_5	$-C_2H_5$ H_5C_2-	Li	70
CH_3	$-(CH_2)_5-$	MgBr	53
C_2H_5	$-(CH_2)_5-$	MgBr	59

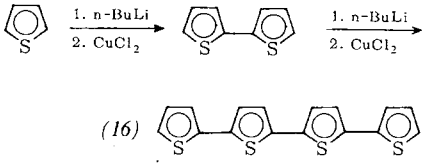
[a] In this experiment the molar ratio *(13)*/CuCl = 1 : 0.2, otherwise *(13)*/Cu halide = 1 : 1.

In the couplings with $CuCl/O_2$, the first phase yields a crystalline copper(I) compound that is sparingly soluble in 1,2-dimethoxyethane/ether (1 : 1) and that was isolated in a yield of 95% in one case [*(13)*, R = C_6H_5, 2R' = $-(CH_2)_5-$, M = Li][34]. Oxygen reacts exothermally with this compound at 20 °C to form yellow copper complexes, from which the organic ligands *(15)* can be liberated only by treatment with KCN/KOH, glycine, or concentrated NH_3. The copper complexes are so stable that no copper ions are liberated during the reaction. Unlike in the coupling of ketimines (cf. Section 3.1.3) and of unsubstituted amidines (cf. Section 4.4.2), therefore, this coupling cannot be carried out with *catalytic* quantities of CuCl (Table 5, 2nd experiment).

It has been shown for *(14)*, R = C_6H_5, 2R' = $-(CH_2)_5-$, that *free* N^1,N^1-dialkylated amidines can also be coupled with one equivalent of CuCl and oxygen in 1,2-dimethoxyethane at 85 °C to form compounds *(15)*. However, the yield was only 10 %[32].

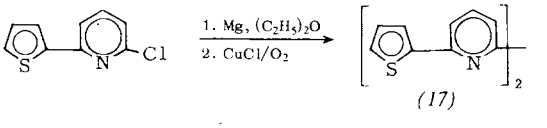
3.2. Dihetarene and Polyhetarenes Syntheses

Hetarenes of the nucleophilic type ("excess of π electrons") are readily accessible to oxidative coupling, since copper can be conveniently introduced by hydrogen-lithium exchange followed by transmetalation. On reaction of thiophene with *n*-butyllithium[35] and then with one mole of $CuCl_2$, 2,2'-bithienyl was formed in 54% yield[36]; when 2 mol of $CuCl_2$ were used the yield was increased to 85 %[37]. Repetition of the coupling led in a yield of 64 % to quaterthiophene *(16)*[38]; further coupling of this product has not yet been achieved[38, 39]. The other compounds in Table 6 were obtained in a similar manner.



(16)

Hydrogen-metal exchange is not generally possible in hetarenes of the electrophilic type ("deficiency of π electrons"). The halides were therefore used as the starting materials for the introduction of copper, which was carried out by halogen-lithium exchange or by formation of a Grignard compound, followed by transmetalation. In addition to 2,2'-bipyridyl and its derivatives (Table 7), the compound *(17)* containing four hetarene rings was also synthesized, but only in a 5 % yield[41].



(17)

When CuCl is used the reaction yielded deep-colored pyridylcopper(I) compounds, which were stable in THF/ether at +60 °C, and oxidation with oxygen was necessary to initiate the coupling (20 °C). On the other hand the red pyridylcopper(II) compounds obtained with $CuCl_2$ or $CuBr_2$ in solution decomposed even at 0 °C, with almost quantitative formation of the coupling products (Table 7).

3.3. Cyclopolyarene Syntheses

The cyclopolyarenes known at present were mostly prepared by oxidative coupling *via* organometallic compounds of transition metals; here again copper was found to be particularly favorable. Two syntheses in which organocopper compounds were postulated as intermediates[48, 49] are the following:

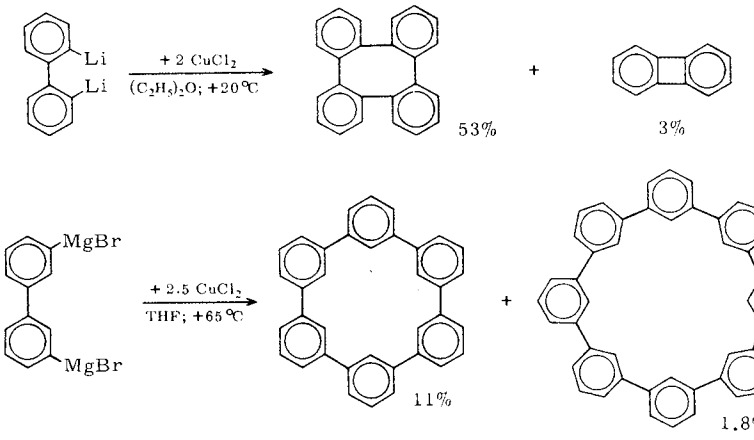
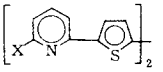
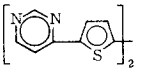
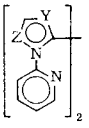
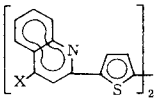
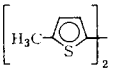
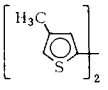
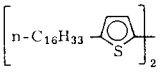


Table 6. Oxidative coupling of nucleophilic hetarenes. The linkage point in every case is in the center of the molecule. T_{max} = maximum reaction temperature. The introduction of lithium was carried out at −60 to 0 °C.

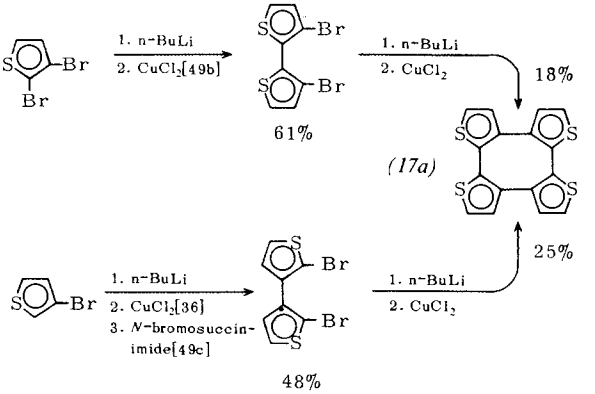
Li-reagent	mol $CuCl_2$	T_{max} [°C]	Product		Yield [%]	Ref.
n-BuLi [35]	2	66 [a]		X = S	85	[37]
	1	35 [b]		X = O	42	[40b]
	1	66 [a]		X = NCH_3	30	[40b]
	1	35 [b]	*(16)*		64	[38]
t-BuLi	1	66 [a, c]		X = H	63	[40c, 41]
n-BuLi	1	66 [a]		X = Cl	82	[40c, 41]
$LiN(iPr)_2$	5	35 [b]			6	[42]
n-BuLi	2	46 [d]		Y = CH, Z = N	21	[40a, 43]
	2	46 [d]		Y = N, Z = CH	18	[40a, 43]
	2	46 [d]		Y = Z = N	18	[40b, 43]
	2	46 [d]		X = H	14	[44, 45]
	2	140 [e]		X = *n*-C_9H_{19}	24	[46]
	1	35 [b]			54	[38]
	1	35 [b]			25	[38]
	2	66 [a]			66	[46]

[a] In THF.
[b] In ether.
[c] Coupling with $CuCl/O_2$.
[d] In ether/THF (1 : 1).
[e] As [b], then diethyl ether evaporated off under reduced pressure and residue dissolved in di-*n*-butyl ether.

Table 7. Coupling of pyridine derivatives (for conditions see text) [47].

Pyridine derivative employed	Reagents	Product	Yield [%] [a]
2-bromo-	$BuLi/CuCl_2$	2,2'-bipyridyl	61 (90)
	$BuLi/CuCl/O_2$		44
	$Mg/CuCl/O_2$		29
3-bromo-	$BuLi/CuBr_2$	3,3'-bipyridyl	48 (98)
	$Mg/CuCl/O_2$		44
4-chloro-	$Mg/CuCl/O_2$	4,4'-bipyridyl	37
2,6-dibromo-	$BuLi/CuBr_2$	6,6'-dibromo-2,2'-bipyridyl	35 (90)

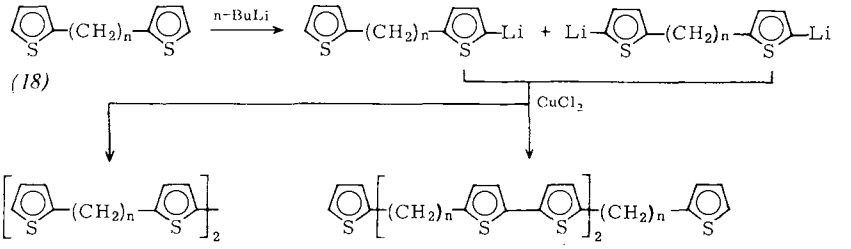
[a] In brackets: yields based on the intermediate lithiopyridines, the quantities of the latter being determined by interception with CO_2 or benzaldehyde.



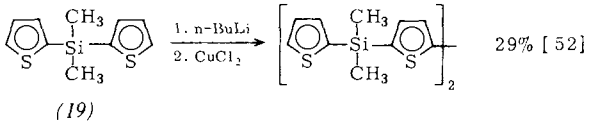
Recently we have been able to prepare the heterocyclic cyclotetraarene *(17a)* by twofold oxidative coupling *via* two different routes[49a].

3.4. Protophane and Heteraprotophane Syntheses

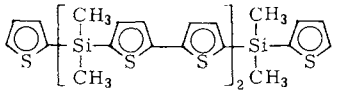
The oxidative coupling of dihetarylalkanes (alkylene-dihetarenes) and dihetarylsilanes provides a very suitable method for the preparation of protophanes and heteraprotophanes (cf. also Section 4.5.2; for nomenclature cf.[50]). On introduction of copper by the metalation/transmetalation route, *(18)*, *(19)*, and *(20)* each give a mixture of tetranuclear and hexanuclear coupling products, since a monolithium compound and a dilithium compound are both formed in the reaction with one mole of *n*-butyllithium. An octanuclear coupling product is also formed from *(20)*.

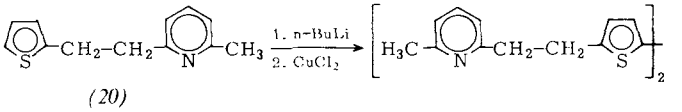


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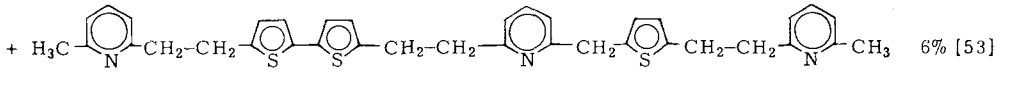


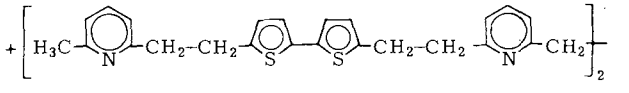
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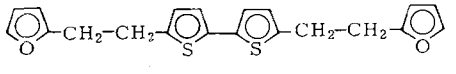


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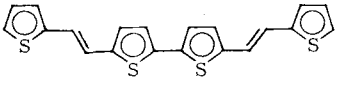




On the other hand, 1-(2-furyl)-2-(2-thienyl)ethane[54] and *trans*-1,2-di(2-thienyl)ethylene[51] each give only a tetranuclear protophane [*(21)* and *(22)* respectively], since the metalation leads almost exclusively to the monolithium compound in these cases, owing to differences in acidity of the hetaryl



(21) 43%



(22) 28%

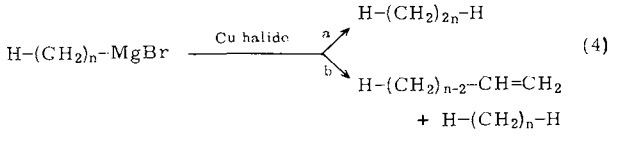
residues or delocalization of the negative charge over the entire molecule.

4. Linkage of C or N Atoms with sp^3 Hybridization

4.1. Alkane Syntheses

According to literature data, isopentylmagnesium bromide reacts with $CuCl_2$ in ether at about -10 °C to give the coupling product 2,7-dimethyloctane in a yield of more than 60%[55], whereas the reaction of ethylmagnesium bromide with CuCl in the same solvent at 0 °C leads exclusively to ethylene and ethane[56]. How can such different reactions occur?

In our experience, when copper halides are allowed to act on alkylmagnesium halides, as shown in eq. (4), the coupling a) and the disproportation b) generally proceed simultaneously. It is probable that the disproportionation is generally initiated by β-elimination of a copper hydride species from the intermediate organocopper compound, and must



(4)

always be expected if there is an H atom vicinal to the Cu atom as in *(25)* (see below).

Whitesides et al.[57] conclusively demonstrated the copper hydride elimination in the thermolysis of *n*-butyl(trioctylphosphane)copper(I), and postulated the reaction in accordance with eq. (5). The (autocatalytic) disproportionation of ligands of alkylcopper(I) compounds that are not complexed with a phosphane appears to proceed in a similar manner[58].

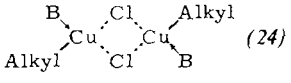
$$\begin{aligned}&CH_3{-}CH_2{-}CH_2{-}CH_2{-}Cu{\leftarrow}P(C_8H_{17})_3 \rightarrow\\ &CH_3{-}CH_2{-}CH{=}CH_2 + HCu{\leftarrow}P(C_8H_{17})_3\\ &CH_3{-}CH_2{-}CH_2{-}CH_2{-}Cu{\leftarrow}P(C_8H_{17})_3 + HCu{-}P(C_8H_{17})_3 \rightarrow\\ &CH_3{-}CH_2{-}CH_2{-}CH_3 + 2\,Cu + 2\,P(C_8H_{17})_3\end{aligned} \qquad (5)$$

The disproportionation, which leads to a lower yield of the coupling product, can be suppressed in several ways:

a) The coupling proceeds to a relatively large extent (14 to 88%) if alkylcopper(I) compounds are converted into cuprate complexes *(23)*. Because of the relatively high thermal stability of these compounds, in which the alkyl residues are obviously favorably arranged for the linkage, oxidation with oxygen is necessary for the coupling. Cyclizations have also been achieved (25—30% yield)[7].

$$\begin{matrix}\text{Alkyl–Cu}\\ +\\ \text{Alkyl–Li}\end{matrix} \rightarrow [\text{Alkyl–}\overset{\ominus}{\text{Cu}}\text{–Alkyl}]\ \overset{\oplus}{\text{Li}}$$

(23)



(24)

b) According to our investigations, low temperatures and $CuCl_2$ favor the coupling, whereas higher temperatures and CuCl favor the disproportionation (Fig. 1). The sudden change in the yield at about −5 °C in the reaction of octylmagnesium bromide with $CuCl_2$ (Fig. 1) suggests that the coupling takes place in alkylcopper halide aggregates that progressively decompose with rising temperature, *e.g.* to form *(24)*[59] or monomers, which are less favorable for the coupling[60] (B = diethyl ether).

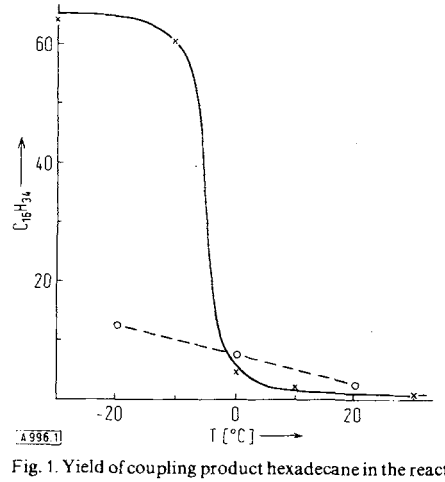
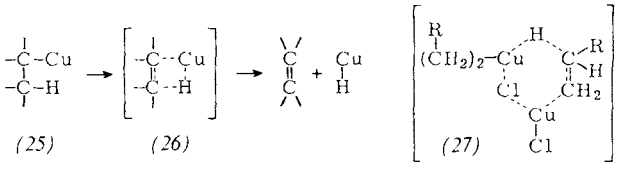


Fig. 1. Yield of coupling product hexadecane in the reaction of octylmagnesium bromide in ether with one mole of $CuCl_2$ (——) or CuCl (----) as a function of the reaction temperature [60].

c) The alkyl residue also has a strong influence on the coupling/disproportion ratio; according to Table 8, the coupling component is much higher for the cyclohexyl residue than for cyclopentyl or octyl. The conditions are thus similar to those in the oxidative coupling of secondary amines (cf. Section 4.2). Since *syn* eliminations with coplanar transition states are much less favorable energetically for the cyclohexyl residue, because of its more stable chair conformation, than for the cyclopentyl residue or for open-chain alkanes[61], the exceptional position of the cyclohexyl residue is best explained by the assumption that the disproportionation is introduced by a *syn*-coplanar β-elimination of copper hydride, and is therefore inhibited in the cyclohexylcopper compounds. The most likely transition state for the *syn* elimination of copper hydride is *(26)*, though six-center transition states such as *(27)* are also conceivable.



(25) *(26)* *(27)*

Cu = Cu^I or Cu^{II}

Table 8. Reaction of alkylmagnesium bromides RMgBr with one mole of $CuCl_2$ (yields in brackets: with CuCl) in ether at 0 °C [60] to form the coupling product (R—R) and the disproportionation products alkane (RH) and alkene.

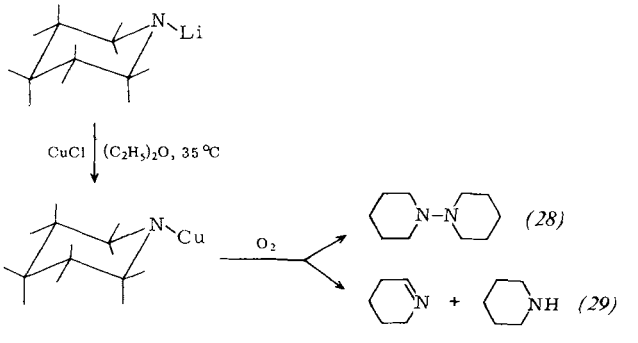
R	Yield [%] R—R	alkane	alkene
octyl	9 (3)	47 (47)	43 (49)
cyclohexyl	58 (26)	21 (39)	21 (34)
cyclopentyl	1	46 [40b]	42 [40b]

4.2. Synthesis of Hydrazine Derivatives

Reactions of *N*-chlorodialkylamines with finely divided copper led to azomethines instead of to the expected tetraalkylhydrazines[62]. Since copper dialkylamides, as shown below, tend to form azomethines, it is probable that the reaction initially gives compounds of this type.

If copper dialkylamides are formed from the lithium amides by transmetalation in boiling ether, hydrazine derivatives are formed as well as azomethines[27,63], but only from six-membered cyclic amines in the cases investigated by us (Table 9)[64,65]. Because of the relatively high thermal stability of the copper(I) amides, the lithium amides must be treated with $CuCl_2$ or $CuCl/O_2$ here.

In the most thoroughly investigated reaction of $CuCl_2$ with lithium piperidide, in addition to the hydrazine derivative *(28)* and the azomethine *(29)*, piperidine is formed in an equimolar quantity with respect to *(29)*. As in the case of



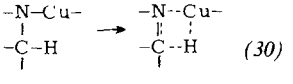
alkylcopper compounds, therefore, disproportionation of the ligands occurs as well as the coupling.

Table 9. Reaction of amines and lithium amides with $CuCl/O_2$ to form hydrazine derivatives and azomethines in ether at 35 C [63].

Li amide	Cu halide: Li amide: free amine	Yield [%] [a] coupling product	azomethine
Li piperidide	1:1:20	110 [c]	60
	(1:2:20) [b]	(59)	(53)
	1:1:2	29	34
	(1:1:0) [d]	(8)	(14) [e]
Li morpholide	1:1:9.5	80	—
Li pyrrolidide	1:1:9.5	—	278 [c]
Li diethylamide	1:1:7.2	—	31
Li (*N*-methylanilide)	1:1:6.6	—	(polymerization)

[a] Yield based on lithium amide.
[b] Because of the stoichiometric proportions, a cuprate complex is probably formed in this case.
[c] The yield of more than 100% shows that piperidine and pyrrolidine respectively are included in the coupling process.
[d] With $CuCl_2$.
[e] 15% of piperidine is also formed.

This disproportionation, which normally predominates over the coupling, appears to be energetically unfavorable in the case of copper compounds of six-membered cyclic amines (piperidine, morpholine). This corresponds exactly to the situation in the alkylcopper compounds (cf. Section 4.1), and can be explained in a similar manner, *i.e.* by hindrance of a concerted *syn*-β-elimination of a copper hydride species [transition state *(30)*?] because of the relatively stable chair conformation of the ring system. In the case of morpholine ("4-oxapiperidine"), for some reason that has not yet been found, this elimination evidently does not occur at all.

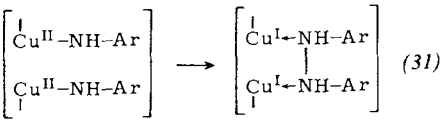


(30)

The air oxidation of *free* piperidine in the presence of CuCl (in ether at 35 °C) leads only to a small extent to the coupling product *(28)* (1%) and the azomethine *(29)* (5%).

4.3. Synthesis of Azo Compounds

Primary arylamines are oxidized to azo compounds by oxygen in the presence of CuCl[13]. It is assumed that an aggregated arylaminecopper(II) compound is converted into a hydrazobenzenecopper(I) complex *(31)* (dicentric ligand coupling),



(31)

Table 10. Oxidation of hetarylamines with $CuCl/O_2$ to form azo compounds (in pyridine at 20 °C) [67].

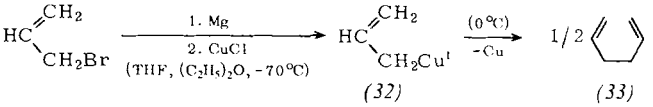
Amine	Yield [%]
2- and 4-aminopyridine	0
3-aminopyridine	27
3-aminoquinoline	29
2-aminothiazole	27

whose organic component is then dehydrogenated to the azo compound[66]. We have coupled some hetarylamines in a similar manner (Table 10)[67].

4.4. Coupling of Compounds Containing Allyl and Heteroallyl Groups

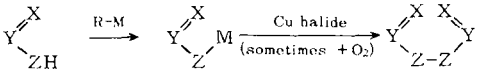
4.4.1. Couplings without Secondary Reactions

Wilke[68] described the coupling of allyl groups bonded to nickel. The resulting 1,5-hexadiene ("bisallyl") *(33)* was also obtainable (99%) *via* allylcopper(I) *(32)*, which occurs as a yellowish precipitate[69].



(32) *(33)*

In view of the practically quantitative yield in this coupling, attempts were made to see whether similar smooth coupling is possible with heteroallyl ligands (Tables 11, 12, and 13). The couplings proceeded in accordance with eq. (6), and were followed by secondary reactions in some cases (Table 13).



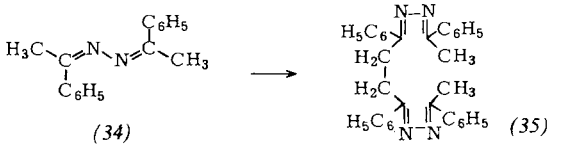
(6)

M = alkali metal or MgBr

Almost quantitative coupling was achieved only for the 1-azaallyl group (Table 11). The coupling was particularly poor for the groups containing oxygen. Since heteroallylcopper(I) compounds are more stable than allylcopper(I), copper(I) halide/O_2 or copper(II) halide was necessary in most cases as the coupling reagent. In the case of the amides (1-oxa-3-azaallyl group), the result was satisfactory only when copper(II) halide/O_2 was used; it is possible that copper(III) compounds occur here as intermediates.

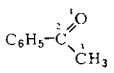
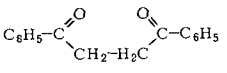
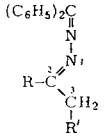
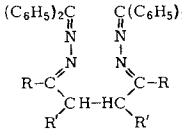
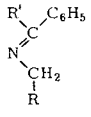
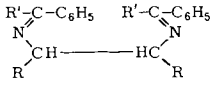
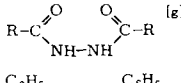
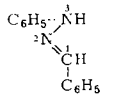
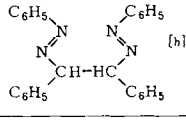
A number of findings call for further explanation. According to Table 11 the 1,4-diketone dibenzoylethane was formed in a yield of only 11% from *acetophenone*[70] (even lower yields with $CuCl/O_2$ or $CuCl_2$). However, the yield increased to about 75% when acetophenone was converted into a *ketazine* by reaction with benzophenone hydrazone, the coupling product of the ketazine (Table 11) being hydrolyzed with hydrochloric acid[71]. It is therefore helpful to mask acetophenone, and presumably aryl methyl ketones in general, with the grouping $=N-N=C(C_6H_5)_2$ for the oxidative coupling.

Acetophenone azine *(34)*, which is not listed in Table 11, and which has two points of attack available for the coupling, reacted with one mole of lithium diisopropylamide and one mole of $CuCl/O_2$ to form the dehydrodimer *(35)* (54%) as well as polymeric compounds. Intramolecular coupling of



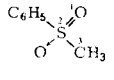
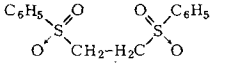
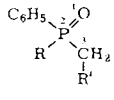
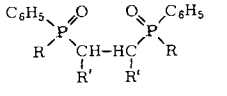
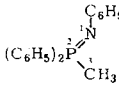
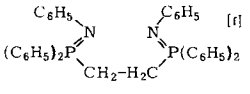
(34) *(35)*

Table 11. Oxidative coupling of compounds containing a 1-oxa-, 1-aza-, 2-aza-, 1-oxa-3-aza-, or 2,3-diazaallyl group (from top to bottom). T_{max} = maximum reaction temperature.

Reactant	Alkali-metalation with	Trans-metalation and coupling with	T_{max} [°C]	Product		Yield [%]	Ref.
	$NaNH_2$ [a]	CuCl [b]	20			11	[70, 71]
	$LiN(iPr)_2$ [b]	$CuCl/O_2$ [b]	60		$R=C_6H_5$, $R'=H$ R = 1-naphthyl, $R'=H$ $R=C_6H_5$, $R'=CH_3$ [f] $R=C_6H_5$, $R'=C_2H_5$ [f] $R-R'=-(CH_2)_4-$ [f]	96 80 57 76 53	[72] [72] [72] [72] [72]
	$NaNH_2$ [c] $NaNH_2$ [c] $LiN(iPr)_2$ [b]	CuI [c] CuCl [a] CuCl [d]	50 50 60		$R=C_6H_5$, $R'=H$ [f] $R=C_6H_5$, $R'=CH_3$ [f] $R=H$, $R'=C_6H_5$	57 32 31	[73, 74, 77] [73, 74, 77] [73, 74, 77]
	$NaNH_2$ [e]	$CuBr_2/O_2$ [d]	67	 [g]	$R=C_6H_5$ $R=n\text{-}C_5H_{11}$ $R=CH_3$	29 24 0	[23, 75] [23, 75] [23, 75]
	$NaNH_2$ [b]	$CuCl/O_2$ [c]	60	 [h]		59	[70, 75]

[a] In ether.
[b] In THF/ether.
[c] In 1,2-dimethoxyethane.
[d] In THF.
[e] In benzene.
[f] The *meso* and *racem* forms (1 : 1) are obtained in every case.
[g] Poorer yields with $CuBr_2$ alone, no coupling with $CuCl/O_2$.
[h] The melting point suggests the presence of the *meso* form having the structure indicated, which was described by *T. W. Milligan* and *B. C. Minor*, J. Org. Chem. *27*, 4663 (1962). This information is used to correct a structure given in an earlier publication [75].

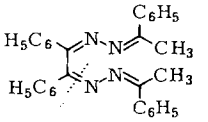
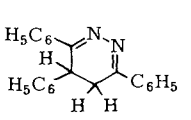
Table 12. Oxidative coupling of compounds containing a 1-oxa-2-thia, 1-oxa-2-phospha-, or 1-aza-2-phosphaallyl group (from top to bottem). T_{max} = maximum reaction temperature.

Reactant	Initial metalation with	Trans-metalation and coupling with	T_{max} [°C]	Product		Yield [%]	Ref.
	C_2H_5MgBr [a]	$CuCl/O_2$ [b]	20			21	[70, 77]
	C_6H_5Li [a]	$CuBr_2$ [c]	60		$R=C_6H_5$, $R'=H$ [d] $R=R'=C_6H_5$ $R=C_6H_5$, $R'=CH_3$ $R=C_6H_5$, $R'=n\text{-}C_3H_7$ $R=R'=CH_3$	48 34 4 6 35	[70] [25] [25] [25] [25]
	C_6H_5Li [c, e]	$CuBr_2$	60	 [f]		30	[25]

[a] In ether.
[b] In THF/benzene/ether.
[c] In THF/ether.
[d] With CuCl instead of $CuBr_2$, the reaction led to an orange copper(I) compound that was stable in THF at 60°C and reacted rapidly with oxygen at 20°C with ligand coupling (42%).
[e] A 1-aza-2-phosphaallyllithium compound (orange in THF) was obtained here for the first time (yield 50%, determined by reaction with benzaldehyde and with D_2O) [25].
[f] This coupling product was very sensitive to hydrolysis and could not be obtained in the pure state. It was hydrolyzed by hydrochloric acid to the known bis-(phosphane oxide) [25].

(35) on the methyl group was not possible even on application of the dilution principle[25].

A similar cyclization attempt with *(36)* also failed to give the expected ten-membered ring. Fragmentation occurred, with formation of the known[76] dihydropyridazine *(37)* (17%)[25].

(36)   *(37)*

The *azomethines* (2-azaallyl compounds) listed in Table 11 can be readily obtained from amines by known methods, and their coupling products can be smoothly degraded to 1,4-diamines by acid hydrolysis. The coupling of these azomethines thus allows diamine syntheses in accordance with the scheme

$$2R{-}CH_2{-}NH_2 \rightarrow R{-}CH(NH_2){-}CH(NH_2){-}R.$$

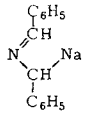
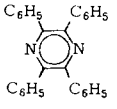
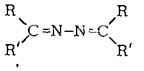
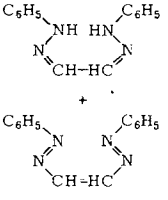
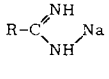
The group =CR'R'' acts here as a masking group.

pounds were stable at room temperature. These stable organocopper(I) compounds are very promising reagents for additions to unsaturated compounds and substitutions on reactive halides[78] similar to corresponding reactions in Tables 1 and 2[79].

4.4.2. Couplings with Secondary Reactions

Some couplings (Table 13) are followed by secondary reactions (elimination, isomerization, dehydrogenation, cyclization with aromatization):

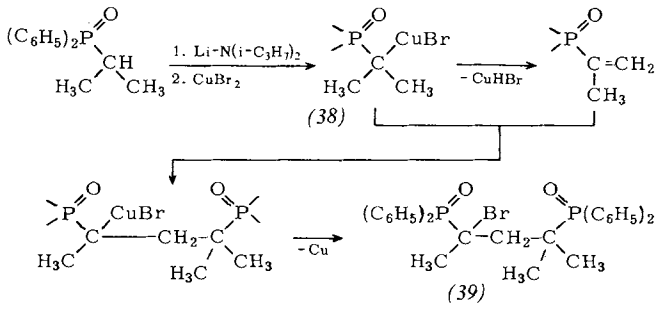
Table 13. Oxidative couplings of heteroallyl compounds associated with secondary reactions. T_{max} = maximum reaction temperature.

Reactant	1st intermediate	Transmetalation and coupling with	T_{max} [°C]	Product		Yield [%]	Ref.
N-Benzylidenebenzylamine + $NaNH_2$		$CuBr_2$ [a]	35	 *(41)*		20	[70, 73]
Hydrazone + $NaNH_2$		$CuCl/O_2$ [a]	20–30		$R=R'=CH_3$	46	[71, 75]
					$R=H, R'=C_6H_5$	30	[71, 75]
Methylphenyldiimine + *n*-BuLi		$CuCl/O_2$ [b]	−20			30	[29]
						30	[29]
Nitriles + $NaNH_2$		$CuCl$ [b]	85		$R=C_6H_5$	0	[80]
		$CuCl_2$ [b]			$R=C_6H_5$	32	[80]
		$CuCl/O_2$ [b]			$R=C_6H_5$	45	[80]
		$CuCl_2/O_2$ [b]			$R=C_6H_5$	74	[80]
		$CuCl_2/O_2$ [b]			$R=p$-Tolyl	47	[80]
		$CuCl_2/O_2$ [b]			R = 2-Naphthyl	30	[80]

[a] In ether.
[b] In 1,2-dimethoxyethane.

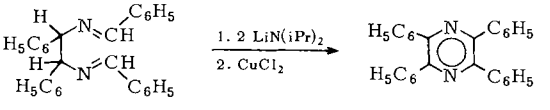
In experiments on the coupling of phosphane oxides (Table 12) the coupling products were formed in a yield of less than 10% when the intermediate organocopper compound satisfied the constitutional condition for the β-elimination of copper hydride. This is especially so (six H atoms vicinal to Cu) in the hypothetical intermediate *(38)*. Significantly only the anomalous product *(39)* (11%), which could have been formed by the indicated route, was obtained in this case[25].

Where the couplings in Tables 11 and 12 were not carried out exclusively with copper(I) halides, the heteroallylcopper(I) com-



(38) *(39)*

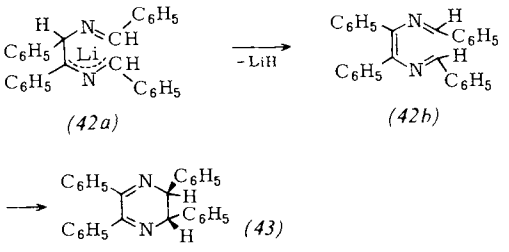
(40) may be regarded as an intermediate in the formation of *2,3,5,6-tetraphenylpyrazine (41)* (Table 13), since the *meso* form of *(40)* has been cyclized to *(41)* in 11% yield by the action of lithium diisopropylamide and $CuCl_2$ (in ether at 20 °C)[74].



(40) *(41)*

Copper is presumably only indirectly involved in the actual cyclization step, since the cyclization *(40)*→*(41)* also proceeded, though in a somewhat lower yield (4%), with lithium diisopropylamide alone. *trans*-2,3-Dihydro-2,3,5,6-tetraphenylpyrazine *(43)* was formed as a by-product (7%). It seems reasonable to conclude that the 2,5-diazatriene *(42b)* is formed *via (42a)* and reacts electrocyclically to form *(43)*[74].

In the couplings leading to *s-triazoles*, it was unnecessary to add strong complexing agents to the reaction mixture to



(42a) (42b) (43)

with eq. (7) to 1,2-dihetarylethanes (ethylenedihetarenes). The yields are good even when the organocopper intermediate has a structure that would allow the β-elimination of a copper hydride species (Table 14, experiments 2—4, and 7).

Anomalous linkage was never observed in these couplings. In the reaction of 2-lithiomethylpyridine with $CoCl_2$ (*via* free radicals?), on the other hand, the anomalous coupling products *(44a)* (10%) and *(44b)* (2%) were formed as well as 2,2'-ethyl-

Table 14. Coupling of alkylhetarenes in accordance with eq. *(7)*. [Introduction of lithium with *n*-BuLi or C_6H_5Li, transmetalation with CuCl (yields in brackets: with $CuBr_2$); addition of 1 to 1.1 mol of CuCl at −10 to 0°C to the solution of the organolithium compound. The mixture was generally then warmed to 50—60°C.]

No.	X	R	Yield [%]	Ref.	*meso* *racem*
1	2-pyridyl [a]	H	72 (78)	[82, 84a]	—
2		CH_3	63	[47, 82]	1:1.9
3		C_2H_5	69	[47]	1:3.0
4		i-C_3H_7	63	[84b]	1:3.4
5		t-C_4H_9	0	[84b]	—
6		C_6H_5	69	[47, 82]	?
7	4-methyl-2-pyridyl [a]	H	73	[84c]	—
8	6-methyl-2-pyridyl [a]	H	71 (77)	[82, 84a]	—
9	6-ethyl-2-pyridyl [b, c]	H	63	[84c]	—
10	4-pyridyl [a]	H	54	[47, 82]	—
11		CH_3	40	[47, 82]	?
12		C_2H_5	34	[47, 82]	?
13		C_6H_5	65	[47, 82]	?
14	2-quinolyl [d]	H	67 (69)	[32, 82]	—
15	4-quinolyl [d]	H	58	[32, 82]	—
16	2-phenyl-4-quinolyl [d]	H	74	[32, 82]	—
17	3-methyl-2-quinoxalinyl [d]	H	61	[32, 82]	—

[a] In THF/diethyl ether (approx. 1:1).
[b] In anisole.
[c] Transmetalation with $CuCl_2$.
[d] In 1,2-dimethoxyethane/diethyl ether (approx. 1:1).

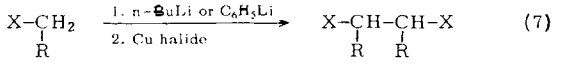
liberate the organic reaction product. The copper complexes formed by coupling are therefore labile. Accordingly, unlike in the coupling of *N,N*-dialkylated amidines (cf. Section 3.1.4), it was possible to convert sodium benzamidide into 3,5-diphenyl-*s*-triazole with no serious decrease in yield (28%) by the use of oxygen and a *catalytic* quantity (0.1 mol) of CuCl[80].

1,3-Diazaallylcopper compounds are formed as intermediates in these couplings. One of these, copper(I) benzamidide[81], has been isolated (80%) after the reaction of sodium benzamidide with CuCl in 1,2-dimethoxyethane at 20—35°C. This yellow compound, which is insensitive to air in the dry state, and which is more easily obtainable by reaction of benzamidine with CuCl in aqueous ammonia solution, reacts with oxygen at 85°C in 1,2-dimethoxyethane to form 3,5-diphenyl-*s*-triazole (45%)[80].

4.5. Synthesis of Dihetarylethanes, Protophanes, and Phanes

4.5.1. Dihetarylethanes

The oxidative coupling *via* organocopper compounds is a suitable method for the linkage of alkyl groups attached to electrophilic hetarenes[82, 83]. The reaction leads in accordance



(7)

X = Hetaryl

enedipyridine (1,2-di(2-pyridyl)ethane) (11%)[47]. 2-Lithiomethylpyridine reacts in ether with $FeCl_2$, $FeCl_3$, and $NiCl_2$, in the same way as with copper halides to give exclusively 2,2'-ethylenedipyridine (51, 44, and 44% respectively)[47].



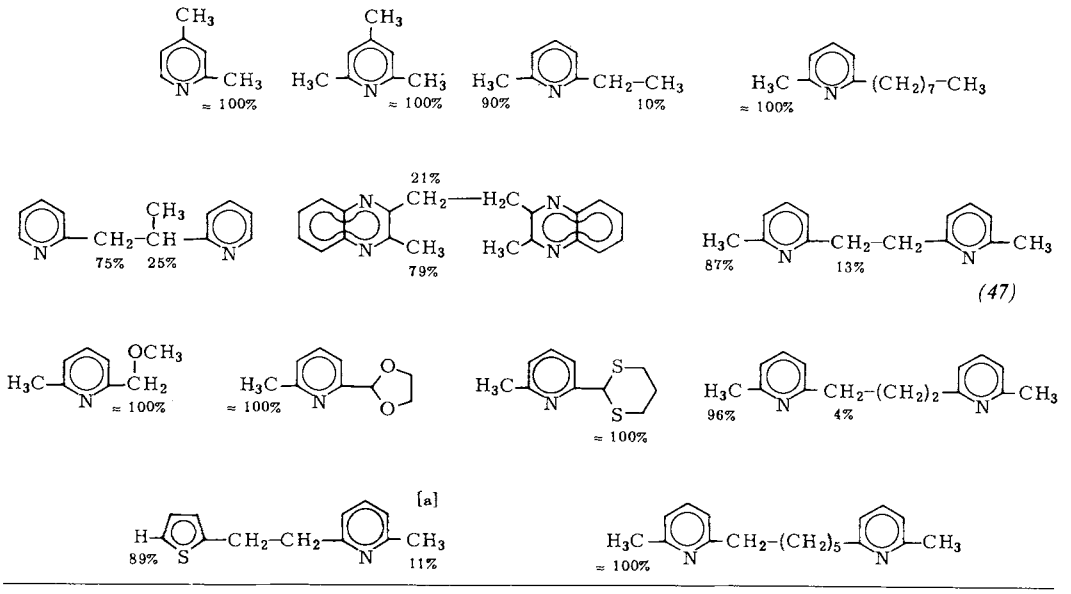
(44a) *(44b)*

Where *meso* and *racem* forms can occur, both are formed. The (lower-melting) *racem* form is favored when R = alkyl (Table 14, experiments 2—4) and is increasingly favored with increasing size of the alkyl residue. The preferential formation of the *racem* form is evidence against the occurrence of free radicals, since the (higher-melting) *meso* form is preferentially obtained in the peroxide-initiated free-radical dehydrodimerization of 2- and 4-alkylpyridines[85].

Since lithium can be introduced regioselectively even into more complicated alkylpyridines at low temperatures (Table 15), and experience so far has shown that the metalation position does not change on transmetalation with copper halides, preparatively useful couplings are also possible in cases of this nature (cf. Table 14, experiments 7 and 9, and Section 4.5.2).

The alkylpyridines with ether, cyclic acetal, or cyclic dithioacetal groups in Table 15 were coupled to only a small extent, if at all, on reaction of the lithium derivatives with copper

Table 15. Introduction of lithium in the indicated positions, based on the total metalation (=100%), with *n*-BuLi at −70°C in THF [35, 47, 53, 84c, 87].

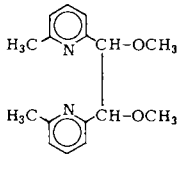
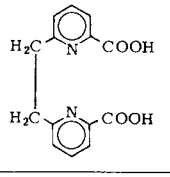
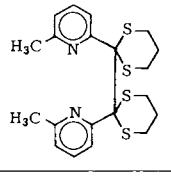
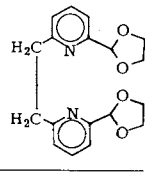


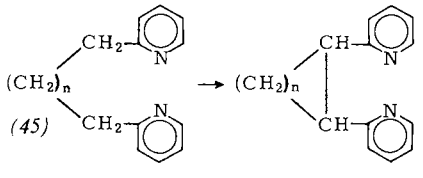
[a] In this case, fast metalation begins only after the addition of tetramethylethylenediamine.

halides or copper halide/O_2. This is probably due to the excessive thermal stability of the organocopper compounds formed. 1,2-Dibromoethane[86] was found to be a better coupling reagent in this case (Table 16)[87].

Intramolecular coupling of α,ω-dipyridylalkanes *(45)* with 2 mol of phenyllithium (approx. 20°C) and 2 mol of CuCl (−50 to +20°C), in THF led to α,β-dipyridylcycloalkanes *(46)*. *(45)*, $n=0$, was dehydrogenated under the same conditions to 2,2'-vinylenedipyridine (1,2-di(2-pyridyl)ethylene)[47, 88].

Table 16. Yield [%] of the indicated product on coupling of corresponding organolithium compounds (in THF [35] at −70 to +70°C in cases 1—3 and at −70 to +20°C in case 4) [87].

No.	Coupling with				
1	CuCl	2	6	0	4
2	$CuBr_2$	6	6	0	11
3	$CuCl/O_2$	12	6	0	18
4	$Br-(CH_2)_2-Br$	32	33	41	34

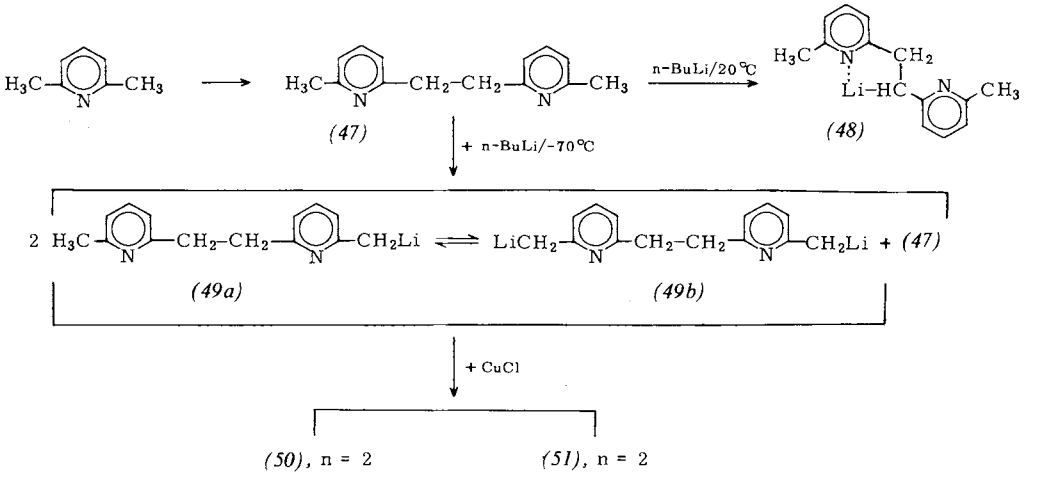


(46), n = 3, 43%; *cis: trans* = 1 : 1

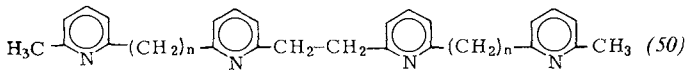
(46), n = 4, 24%; *cis: trans* = 1 : 7

4.5.2. Protophanes

In the case of 2,6-dimethylpyridine, the oxidative coupling *via* organocopper compounds can occur repeatedly, since the



first coupling product 1,2-bis(6-methyl-2-pyridyl)ethane *(47)*, as shown in Table 15, is selectively metalated on the methyl-groups by *n*-butyllithium in THF at −70°C[89,90]. When 1 mol of *n*-butyllithium is used, a mixture of the monolithium and dilithium compounds *(49a)* and *(49b)* is formed. Subsequent reaction of the mixture with CuCl (at −70°C, followed by heating to 60°C) therefore leads to the protophanes *(50)* and *(51)* with $n=2$.


(50)

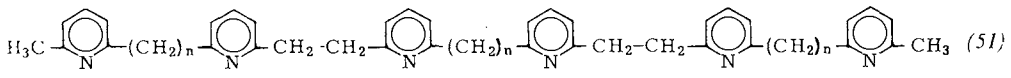
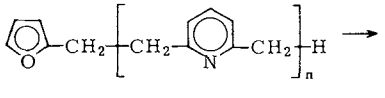
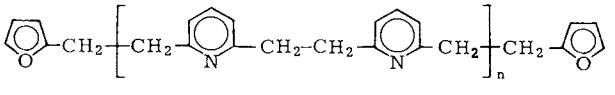

(51)

Table 17. Yields and melting point of pyridinoprotophanes (yields in brackets: coupling with 1,2-dibromoethane instead of with CuCl) [47, 87, 89, 91].

	(50)		*(51)*	
n	Yield [%]	M.p. [°C]	Yield [%]	M.p. [°C]
2	43 (25)	147—148	8 (14)	180—181
3	44 (24)	111—112	8 (13)	142—143
5	46 (22)	79	9 (17)	110—111
6	44 (25)	86	3 (16)	113
8	46 (26)	84	5 (14)	129—130

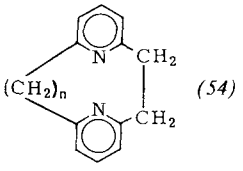
Tetranuclear and hexanuclear protophanes *(50)* and *(51)*, in which shorter ($n=2$) and longer ($n=3$, 5, 6, 8) alkylene segments alternate, were similarly obtained from higher homologs of *(47)*, which are "externally metalated" even more selectively than *(48)*, according to Table 15[91]. Table 17 shows the yields and the melting points, which are sharp. Unlike electrophilic hetaryl residues, nucleophilic hetaryl residues do not favor the lithium-hydrogen exchange in attached alkyl substituents by *n*-butyllithium. The furyl residue also undergoes practically no metalation at low temperatures. It was therefore possible to couple the compounds *(52)* by the action of *n*-butyllithium (in THF at −40°C) followed by CuCl (at −40°C) to form the protophanes *(53)*, which contain different hetarene nuclei[92].

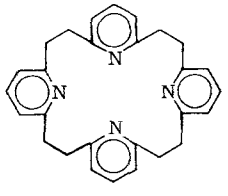

(52), n = 1
n = 2

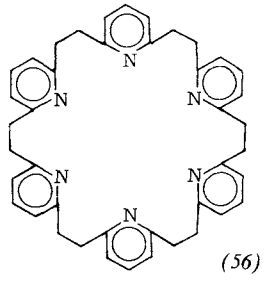

(53), n = 1 (28%)
n = 2 (11%)

4.5.3. Phanes

1,2-Bis(6-methyl-2-pyridyl)ethane *(47)* reacts with 2 mol of *n*-butyllithium to form the dilithium compound *(49b)*. Reaction of the latter with 2 mol of CuCl at −70 to +70°C in THF gave the known[47,93] phanes *(54)*, $n=2$, and *(55)* in yields of only 0.7 and 4% respectively; the octanuclear phane *(56)* was also detectable by mass spectroscopy[47]. Under comparable conditions ($CuCl_2$ instead of CuCl), dilithium compounds homologous with *(49b)* gave the dinuclear phanes *(54)*, $n=3$—6 (yields 2, 15, 3, and 4% respectively)[87,94]. With the exception of *(54)*, $n=4$, the compounds are again formed in low yields despite the application of the dilution principle. With 1,2-dibromoethane as the coupling reagent, however, no phane formation was detected[87].


(54)


(55)


(56)

I am very grateful to the colleagues who took part in the investigations described. May the present review be a lasting reminder of years of shared work.

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Translated by Express Translation Service, London

[1] Protophanes and Polyarenes, Part 13. Part 12: [94].

[2] Cf. *J. E. Gowan* and *T. S. Wheeler*: Name Index of Organic Reactions. Longmans, Green and Co., London 1960.

[3] *M. G. Jaquemin*, Bull. Soc. Chim. Fr. [2] *43*, 556 (1885).

[4] *F. Straus*, Liebigs Ann. Chem. *342*, 201 (1905).

[5] *G. M. Whitesides* and *C. P. Casey*, J. Amer. Chem. Soc. *88*, 4541 (1966); *G. M. Whitesides, C. P. Casey*, and *J. K. Krieger*, *ibid.* *93*, 1379 (1971).

[6] *Th. Kauffmann* and *W. Sahm*, Angew. Chem. *79*, 101 (1967); Angew. Chem. internat. Edit. *6*, 85 (1967).

[7] *G. M. Whitesides, J. SanFilippo, Jr., C. P. Casey*, and *E. J. Panek*, J. Amer. Chem. Soc. *89*, 5302 (1967).

[8] *C. E. Castro, E. J. Gaughan*, and *D. C. Owsley*, J. Org. Chem. *31*, 4071 (1966). Analogous biaryl syntheses: *M. Nilsson*, Tetrahedron Lett. *1966*, 679.

[9] *E. J. Corey* and *G. H. Posner*, J. Amer. Chem. Soc. *89*, 3911 (1967).

[10] *H. O. House, W. L. Respess*, and *G. M. Whitesides*, J. Org. Chem. *31*, 3128 (1966).

[11] *E. J. Corey* and *J. A. Katzenellenbogen*, J. Amer. Chem. Soc. *91*, 1851 (1969).

[12] Cf. *H. R. Christen*: Grundlagen der organischen Chemie. Sauerländer Aarau: Diesterweg-Salle, Frankfurt/M, 1970, p. 625. Absence of free radicals: cf. [5, 15, 16, 60] and Sections 3.1.3 and 4.5.1 of the present article.

[13] *A. P. Terentjew* and *D. Mogilyanski*, Dokl. Akad. Nauk SSSR *103*, 91 (1955); Chem. Abstr. *50*, 4807e (1956); *K. Issleib* and *H. O. Fröhlich*, Chem. Ber. *95*, 375 (1962); *H. Gilman* and *H. H. Parker*, J. Amer. Chem. Soc. *46*, 2823 (1924).

[14] A promising new reagent for metalation with copper is copper(I) *tert*-butoxide; *T. Tsuda, T. Hashimoto,* and *T. Saegusa,* J. Amer. Chem. Soc. *94,* 658 (1972).

[15] *A. Cairncross* and *W. A. Sheppard,* J. Amer. Chem. Soc. *93,* 247 (1970); cf. also *A. Cairncross, H. Omura,* and *W. A. Sheppard, ibid. 93,* 248 (1970).

[16] *F. Bohlmann, H. Schönowsky, E. Inhoffen,* and *G. Grau,* Chem. Ber. *97,* 794 (1964).

[17] Detection of reaction path (1) in an Ullmann reaction: *A. H. Lewin* and *Th. Cohen,* Tetrahedron Lett. *1965,* 4531. On the other hand, some Ullmann reactions follow an Ullmann-like path as follows: ArCu + Ar-X → Ar—Ar + CuX; *P. E. Fanta,* Chem. Rev. *38,* 139 (1946); *64,* 613 (1964).

[18] Cf. *F. Sondheimer* and *Y. Amiel,* J. Amer. Chem. Soc. *78,* 4178 (1956); *F. Sondheimer* and *Y. Gaoni, ibid. 83,* 1259 (1961).

[19] Direct introduction of copper similar to the Ullmann reaction: *Th. Cohen* and *Th. Poeth,* J. Amer. Chem. Soc. *94,* 4363 (1972).

[20] The term "metalation" is used in the present work in its most general sense, and is thus not confined to the hydrogen-metal exchange. The organocopper compounds, which are probably aggregated in general, are always formulated as monomers.

[21] *J. F. Normant* and *M. Bourgain,* Tetrahedron Lett. *1971,* 2583.

[22] *W. Sahm,* Diplomarbeit, Universität Münster 1967.

[23] *A. Schott,* Diplomarbeit, Universität Münster 1967.

[24] *M. Schönfelder,* Dissertation, Universität Münster 1969.

[25] *J. Legler,* Dissertation, Universität Münster 1971.

[26] Lithioaldimines of the type —N=C(Li)— are formed by addition of organolithium compounds to isocyanides (*H. M. Walborsky* and *G. E. Niznik;* J. Amer. Chem. Soc. *91,* 7778 (1969)). Coupling with copper halides to form 1,4-diaza-1,3-dienes has apparently not yet been attempted.

[27] *Th. Kauffmann, J. Albrecht, D. Berger,* and *J. Legler,* Angew. Chem. *79,* 620 (1967); Angew. Chem. internat. Edit. *6,* 633 (1967).

[28] *Th. Kauffmann* and *D. Berger,* Chem. Ber. *101,* 3022 (1968).

[29] *D. Berger,* Dissertation, Universität Münster 1970.

[30] *R. Meyer* and *D. Pillon,* US-Pat. 2870206 (1959); Chem. Abstr. *54,* 1453i (1960).

[31] The mass spectrum contains no molecular peak for *(12).* The most intense molecular peak is that of diphenylmethanimine.

[32] *D. Kuhlmann,* Dissertation, Universität Münster 1969.

[33] The introduction of lithium is unfavorable in the case of the amidines *(13),* R = alkyl, since the lithium compounds largely decompose into nitrile and lithium amide (or α-lithionitrile and amine). No analogous decomposition was observed for the corresponding magnesium compounds [32].

[34] The pale yellow crystals (m.p. 130 °C) contain 1 mol of LiCl, 80% of which can be eluted with anhydrous ethanol [32].

[35] The *n*-butyllithium used in the experiments of my co-workers mentioned in the present review article was commercial material dissolved in *n*-hexane. The small quantity of *n*-hexane that entered the reaction solutions in this way is not mentioned as part of the solvent. Where *n*-hexane is mentioned it was added specially.

[36] *S. Gronowitz* and *H.-O. Karlson,* Ark. Kemi *17,* 89 (1961).

[37] *J. Jackisch,* Dissertation, Universität Münster 1973.

[38] *H.-J. Streitberger,* Diplomarbeit, Universität Münster 1971.

[39] Mechanistic studies on the autoxidation of arylcopper(I) compounds (Ar = phenyl and substituted phenyl): *A. Camus* and *N. Marsich,* J. Organometal. Chem. *46,* 385 (1972).

[40] *J. Legler* (a), *E. Ludorff* (b), *A. Woltermann* (c), and *Th. Kauffmann,* experiments conducted in 1971.

[41] *Th. Kauffmann, E. Wienhöfer,* and *A. Woltermann,* Angew. Chem. *83,* 796 (1971); Angew. Chem. internat. Edit. *10,* 741 (1971).

[42] *B. Greving,* Diplomarbeit, Universität Münster 1972.

[43] *Th. Kauffmann, J. Legler, E. Ludorff,* and *H. Fischer,* Angew. Chem. *84,* 828 (1972); Angew. Chem. internat. Edit. *11,* 846 (1972).

[44] *Th. Kauffmann, J. Jackisch, H.-J. Streitberger,* and *E. Wienhöfer,* Angew. Chem. *83,* 799 (1971); Angew. Chem. internat. Edit. *10,* 744 (1971).

[45] *E. Wienhöfer,* Diplomarbeit, Universität Münster 1971.

[46] *Th. Kauffmann* and *A. Woltermann,* Angew. Chem. *84,* 824 (1972); Angew. Chem. internat. Edit. *11,* 842 (1972).

[47] *W. Sahm,* Dissertation, Universität Münster 1969.

[48] *G. Wittig* and *G. Klar,* Liebigs Ann. Chem. *704,* 91 (1967).

[49] *H. A. Staab* and *F. Binnig,* Chem. Ber. *100,* 293 (1967).

[49a] *Th. Kauffmann, B. Greving,* and *A. Woltermann,* experiments conducted in 1974.

[49b] *S. Gronowitz,* Acta Chem. Scand. *15,* 1393 (1961).

[49c] *R. M. Kellogg, A. P. Schaap,* and *H. Wynberg,* J. Org. Chem. *34,* 343 (1969).

[50] *Th. Kauffmann,* Tetrahedron *28,* 5183 (1972).

[51] *Th. Kauffmann, J. Jackisch, A. Woltermann,* and *P. Röwemeier,* Angew. Chem. *84,* 826 (1972); Angew. Chem. internat. Edit. *11,* 844 (1972).

[52] *H.-H. Kniese,* Diplomarbeit, Universität Münster 1973.

[53] *H. Merten,* Dissertation, Universität Münster, planned for 1974.

[54] *H.-G. Leonhardt,* Dissertation, Universität Münster, planned for 1974.

[55] *E. Sakellarios* and *Th. Kyrimis,* Ber. Deut. Chem. Ges. *57,* 322 (1924).

[56] *H. Gilman, R. G. Jones,* and *L. A. Woods,* J. Org. Chem. *17,* 1630 (1952).

[57] *G. M. Whitesides, E. R. Stedronsky, C. P. Casey,* and *J. SanFillipo, Jr.,* J. Amer. Chem. Soc. *92,* 1426 (1970).

[58] *K. Wada, M. Tamura,* and *J. Kochi,* J. Amer. Chem. Soc. *92,* 6656 (1970).

[59] Dialkylgold(III) halides exist in a similar form in CCl_4 at 25 °C: *A. Burawoy, C. S. Gibson, G. C. Hamson,* and *H. M. Powell,* J. Chem. Soc. *1937,* 1690.

[60] *J. Jackisch,* Diplomarbeit, Universität Münster 1970. Since added styrene is not polymerized and the yields of coupling and disproportionation products are not affected the coupling and disproportionation of the ligands cannot involve free radicals.

[61] Concerning the exceptional position of the cyclohexyl residue in *syn*-β-eliminations and the significance of the dihedral angle in connected eliminations, see: *C. H. De Puy, R. D. Thurn,* and *G. F. Morris,* J. Amer. Chem. Soc. *84,* 1314 (1962); *J. Sicher,* Angew. Chem. *84,* 177 (1972); Angew. Chem. internat. Edit. *11,* 200 (1972).

[62] *F. Klages,* Liebigs Ann. Chem. *547,* 1 (1941).

[63] *J. Legler,* Diplomarbeit, Universität Münster 1967.

[64] *H. Gilman* and *H. H. Parker,* J. Amer. Chem. Soc. *46,* 2823 (1924) tried unsuccessfully to couple diethylamidomagnesium and *N*-methylanilidomagnesium halides with $CuCl/O_2$ to form hydrazine derivatives.

[65] *K. Kirste,* Göttingen, coupled *N*-lithioaziridine in a similar manner to obtain bisaziridine ($CuCl_2$, ether, −50 °C, 0.5% yield; personal communication).

[66] *K. Kinoshita,* Bull. Chem. Soc. Jap. *32,* 777 (1959); Chem. Abstr. *55,* 19741d (1961).

[67] *R. Wirthwein* and *Th. Kauffmann,* unpublished experiments performed in 1970.

[68] *G. Wilke,* Angew. Chem. *75,* 10 (1963); Angew. Chem. internat. Edit. *2,* 105 (1963).

[69] *D. Glindemann* and *Th. Kauffmann,* experiments conducted in 1968.

[70] *Th. Kauffmann, G. Beissner, H. Berg, E. Köppelmann, J. Legler,* and *M. Schönfelder,* Angew. Chem. *80,* 565 (1968); Angew. Chem. internat. Edit. *7,* 540 (1968).

[71] *G. Beissner,* Diplomarbeit, Universität Münster 1968.

[72] *Th. Kauffmann, M. Schönfelder,* and *J. Legler,* Liebigs Ann. Chem. *731,* 37 (1970).

[73] *E. Köppelmann,* Diplomarbeit, Universität Münster 1968.

[74] *E. Köppelmann,* Dissertation, Universität Münster 1971.

[75] *Th. Kauffmann, G. Beissner, E. Köppelmann, D. Kuhlmann, A. Schott,* and *H. Schrecken,* Angew. Chem. *80,* 117 (1968); Angew. Chem. internat. Edit. *7,* 131 (1968).

[76] *J. Sauer, A. Mielert, D. Lang,* and *D. Peter,* Chem. Ber. *98,* 1435 (1965).

[77] *H. Berg* and *Th. Kauffmann,* experiments conducted in 1967.

[78] It is planned to investigate reactions of this type.

[79] Cf. also *J. F. Normant,* Synthesis *1972,* 63; *E. J. Corey* and *J. Kuwajima,* Tetrahedron Lett. *1972,* 487.

[80] *J. Albrecht,* Diplomarbeit, Universität Münster 1967.

[81] Obtained by another route by *E. F. Cornell,* J. Amer. Chem. Soc. *50,* 331 (1928).

[82] *Th. Kauffmann, D. Kuhlmann, W. Sahm,* and *H. Schrecken,* Angew. Chem. *80,* 566 (1968); Angew. Chem. internat. Edit. *7,* 541 (1968).

[83] Strongly electrophilic hetarenes (pyrimidine, pyrazine, pyridazine) are not very suitable for use as activating substituents, since agents for the introduction of lithium and metalation products formed by hydrogen-lithium exchange add to the nuclei. The reaction of benzyl bromide with Mg and $CuCl_2$ to form bibenzyl has been known for a long time.

[84] *H. Schrecken* (a), *W. Sahm* (b), *A. Woltermann* (c), and *Th. Kauffmann,* 1968/71.

[85] *K. K. Chiu* and *H. H. Huang,* J. Chem. Soc. *C 1969,* 2758.

[86] sp^3-C atoms attached to lithium can generally be linked by the use of 1,2-dibromoethane as the coupling reagent, but this reagent fails in the case of sp^2-C atoms attached to lithium (cf. also Section 4.5.3).

[87] *G. Beissner,* Dissertation, Universität Münster 1971, and experiments conducted in 1972.

[88] 1,2-Bis(3-methyl-2-quinoxalinyl)ethane is similarly dehydrogenated to form the ethylene derivative, and not, as was originally assumed [82], cyclized to form a phane [32].

[89] *Th. Kauffmann, G. Beissner, W. Sahm,* and *A. Woltermann,* Angew. Chem. *82,* 815 (1970); Angew. Chem. internat. Edit. *9,* 808 (1970).

[90] When warmed to 20 °C, *(47)* is irreversibly isomerized to the "internally metalated" compound *(48)*, whose higher thermodynamic stability can be explained by the indicated intramolecular coordinate bonding [89].

[91] *Th. Kauffmann, G. Beissner,* and *R. Maibaum,* Angew. Chem. *83,* 795 (1971); Angew. Chem. internat. Edit. *10,* 740 (1971).

[92] *U. Prager,* Diplomarbeit, Universität Münster 1972.

[93] Cf. *W. Backer, K. M. Buggle, J. F. W. McOmie,* and *D. A. M. Watkins,* J. Chem. Soc. *1958,* 3594; *W. Jenny* and *H. Holzrichter,* Chimia *22,* 306 (1968).

[94] *Th. Kauffmann,* Chimia *26,* 511 (1972).

The Pigments of Reddish Hair and Feathers

By R. H. Thomson[*]

Despite sporadic investigations over many years the structures of the pigments responsible for most of the yellow, orange, and brown colors of mammalian hair, and of feathers, have remained unknown. However, recent work has shown that the major reddish-brown pigments, gallophaeomelanins, are polymers containing benzothiazole and tetrahydroisoquinoline units. The yellow-orange and violet trichochromes are minor pigments based on a new chromophore, $\Delta^{2,2'}$-bi(1,4-benzothiazine). Both groups arise *in vivo* from tyrosine and cysteine by a deviation from the biogenetic pathway which normally leads to the formation of eumelanins, the black pigments.

1. Introduction

Plant pigments have been studied intensively over a long period and perhaps 2000 have been accurately documented. Animal pigments are relatively few and not so well defined, and this is particularly true for those which are polymeric, and consequently intractable and difficult to investigate. The hair color of mammals ranges through numerous shades of yellow, orange, and brown, as well as black and white. While the nature of the black pigmentation is now fairly clear[1], until recently little was known about the lighter pigments and the subject was clouded by misleading information and confusing nomenclature.

The omnibus term melanin ($\mu\acute{\varepsilon}\lambda\alpha\varsigma$ = black) is commonly used to describe dark pigments found in animals and plants. In the animal kingdom black pigmentation, widespread in skin, hair, feathers, insect cuticules, melanomas, *etc.*, is attributed to eumelanins ($\varepsilon\tilde{\upsilon}$ = good) while phaeomelanins ($\varphi\alpha\iota\acute{o}\varsigma$ = dusky) cover a broad spectrum from violet to yellow. This is obviously not a satisfactory classification and it is more meaningful to define eumelanins as those pigments found in melanocytes[**] which derive from the tyrosinase oxidation of tyrosine, and phaeomelanins as pigments found in melanocytes which arise by tyrosinase oxidation of tyrosine and subsequent reaction with cysteine. Thus the phaeomelanins, so far found only in feathers and mammalian hair (including so-called red human hair which is really orange), are related biogenetically although they are quite different in structure. They may occur together giving rise to the spots, stripes, and mottled appearance of many animals, and indeed eumelanins and phaeomelanins are jointly responsible for most mammalian coloring. In conjunction with carotenoids, they probably account for most of the colors observed in feathers (blues and greens often arise by diffraction or light scattering in which eumelanins play an important background role). Eumelanins[1] are irregular, crosslinked, polymers, based mainly on 5,6-dihydroxyindole units, and conjugated with protein. These pigments are present in black hair, and various shades of brown, and even blond, hair can be explained by differences in concentration, shape, structure, and oxidation level of the pigment granules.

The distinctive color of "red" hair was at one time ascribed to melanin oxidation products[2]. In 1878 *Sorby*[3] extracted a red pigment from "red" human hair, although the hair still retained its color. This pigment was eventually isolated in 1943 by *Flensch* and *Rothman*[4] who suggested the tentative formula $(C_{15}H_{20}N_2O_9)_2Fe$, and proposed the name "trichosiderin" ($\tau\varrho\iota\chi\acute{o}\varsigma$, $\sigma\acute{\iota}\delta\eta\varrho o\nu$ = hair, iron) "for temporary use until the chemical structure of this compound is established"[*]. In 1956 *Barnicot*[7] showed that "trichosiderin" was an artefact, since extraction of "red" hair with cold dilute alkali yielded an orange-yellow pigment which was converted into the red "trichosiderin" by heating with acid, and later *Boldt* found that the crude pigment obtained by acid extraction could be separated chromatographically into nine[8] components,

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[**] Melanocytes are highly specialized pigment-producing cells.

[*] Although some of the trichosiderin structures have since been established the name was still "temporarily retained" in 1972 [5]. This is abandoned herein in favor of trichochrome [6].

yellow, orange, brown, and violet, some of which were interconvertible. Analysis of these pigments revealed the presence of sulfur but as iron was only detectable in traces the name "trichosiderin" was clearly inappropriate, and these artefacts were named pyrrotricholes ($\pi\upsilon\rho\rho\acute{o}\varsigma$ = fiery).

Parallel with these studies on hair, the red feathers of domestic fowls were also examined[9], and these gave similar mixtures of pigments on acid extraction, but after more than 80 years of sporadic investigation nothing was known of the chemical nature of the pigments in reddish hair and feathers beyond that revealed by indicator properties, electronic spectra, and dubious elemental analyses. However, recent work in Naples has established the structures of the trichochromes, and the general nature of the polymeric gallophaeomelanin pigments is now clear.

2. Recent Work

Chemical investigations on the structure of phaeomelanins commenced at the University of Naples in 1964. In preliminary experiments[10] red feathers from New Hampshire hens were extracted with hot hydrochloric acid which gave a mixture of several red and violet pigments. The presence of nitrogen and sulfur was confirmed but iron was found to be absent although it was detectable in the early stages of purification, and is definitely present in hair. Similar treatment of "red" human hair gave a mixture of four red compounds, in much smaller amount, two of which were identical with two of those obtained from feathers.

Substantially this work confirmed the results of *Boldt*[8] but as some of these pigments are artefacts, and only a small proportion of the total coloring matter is extracted by acid, a mild alkaline extraction procedure was used for subsequent work[11]. Extraction of hen feathers (New Hampshire) with cold 0.1 M NaOH gave a very complex mixture of pigments. They were conveniently divided into two structurally distinct groups by acidification which precipitated the red-brown gallophaeomelanins leaving the minor pigments (trichochromes), which show intense visible absorption, in solution.

3. Trichochromes

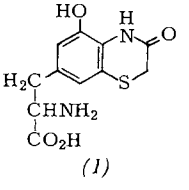
The acid-soluble pigment fraction, after purification on a column of ion-exchange resin and chromatography on Sephadex, was separated into three yellow [B1 (trace), B2 and C1] and two violet pigments [E and F].

Almost from the outset of this investigation *Prota* and *Nicolaus*[10,11] recognized intuitively that the phaeomelanins might be formed *in vivo* by some deviation from the normal course of melanogenesis involving cysteine. A close biogenetical link was apparent from the circumstance that both eumelanins and phaeomelanins are formed in melanocytes, from the operation of a switch mechanism in agoutis[*], and from the consistent 2:1 nitrogen/sulfur ratio in all the feather pigments. In fact, in a very early experiment it was shown that enzymic oxidation[11] of dopa (3,4-dihydroxyphenylalanine, cf. Scheme 3) in the presence of cysteine gave red-brown material closely resembling the gallophaeomelanins. Moreover, when the oxidation was stopped after a short time by acidification, the pale yellow solution changed to violet in a few minutes and it was possible to isolate small amounts of two violet compounds which proved to be identical with the pigments E and F obtained from feathers. Thus from the beginning biogenetic ideas played a predominant role in the structural elucidation studies.

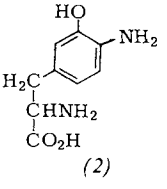
[*] Agoutis are South American rodents which have color-banded hairs, *e.g.*, yellow and black; the pigment distribution between eumelanin and phaeomelanin can change in a very short time.

3.1. Trichochromes B and C

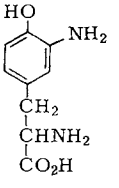
On gentle heating in acidic solution the principal yellow-orange component C (formerly C1) loses carbon dioxide forming a red compound identical with one of the pigments previously obtained by extracting red feathers and hair with hot acid, *i. e.*, decarboxy C is one of the trichosiderins observed by previous workers. Unlike trichochrome C this compound behaves as an indicator, being red in acid (λ_{max} 525 nm) and yellow-orange (λ_{max} 462 nm) in alkaline solution. It possesses two alanyl residues, two phenolic groups and a δ-lactam ring;



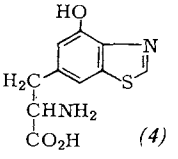
(1)



(2)

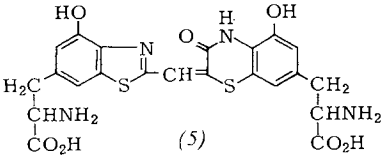


(3)

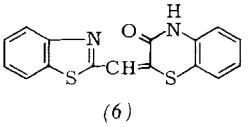


(4)

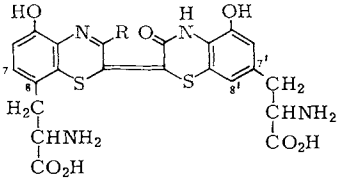
on degradation[12] with hydriodic acid and red phosphorus it gives the amino acids *(1)* and *(2)* [and also a little *(4)*].



(5)

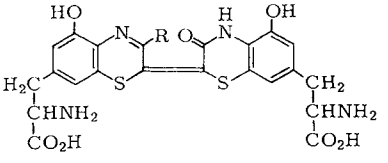


(6)



(7a), R = H

(7b), Trichochrome B, R = CO_2H



(8a), R = H

(8b), Trichochrome C, R = CO_2H

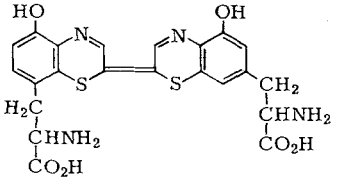
The red compound could therefore be either *(5)* or *(8a)*, and the former was excluded by spectroscopic comparison with the model compound *(6)*. It follows that trichochrome C has structure *(8b)* since its NMR spectrum differs from that of *(8a)* only in the absence of the methine proton signal at $\delta = 9.13$[12]

Trichochrome B (formerly pigment B2) is isomeric with C and has very similar properties. Degradation of the red decarboxy derivative with hydriodic acid gave the amino acids *(1)*, *(2)*, and *(3)*. As *(2)* is formed from *(1)* under these conditions, presumably *(3)* (obtained in very small amount) is derived from an isomer of *(1)*, and accordingly *Prota et al.*[13] formulate this red compound as *(7a)* and trichochrome B as *(7b)*. Thus trichochromes B and C differ solely in the orientation of the alanyl side chains which is fully consistent with biosynthetic studies (see Section 5).

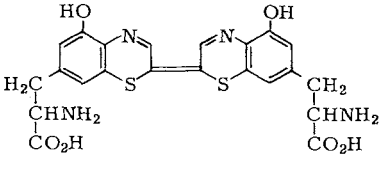
Trichochromes B and C occur in "red" human hair and there is evidence[6] that two other isomers are also present [structures as *(7b)* and *(8b)* but with the alanyl side chains at positions 7,8′ and 8,8′]. The red decarboxylated pigments, obtained by acid extraction, have been identified[6].

3.2. Trichochromes E and F

The two violet pigments in the acid-soluble fraction from feathers have λ_{max} 482nm in alkaline solution, which shifts to 587nm on acidification. Trichochrome F has two alanyl side chains and two phenolic groups but lacks the amide moiety of C, and on heating with hydriodic acid and red phosphorus it gave the amino acids *(2)* and *(4)* (minor component) obtained previously from *(8a)*. On this basis structure *(10)* was proposed[14] for trichochrome F which is in complete accord with its NMR spectrum (the two azomethine protons resonate at $\delta = 8.21$). The isomeric pigment E, available only in very small amount, has the same chromophore as F, and is regarded[14] as *(9)* since degradation in the usual way afforded the isomeric amino acids *(2)* and *(3)*, identified chromatographically.



(9), Trichochrome E

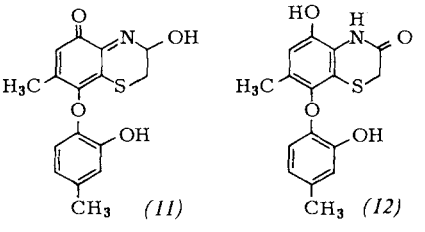


(10), Trichochrome F

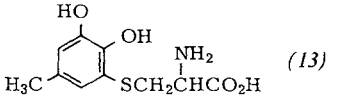
Structures *(9)* and *(10)* were verified by a biogenetic-type synthesis[14]. It will be recalled that small amounts of trichochromes E and F were obtained earlier by oxidizing a mixture of dopa and cysteine. Subsequently it was found that 5- and 2-*S*-cysteinyldopa *(43)* were intermediate products in this reaction, and when a mixture of these was oxidized with alkaline ferricyanide three violet compounds were formed. Two of these were identified, chromatographically, as trichochromes E and F, the third being the symmetrical isomer derived solely from 2-*S*-cysteinyldopa. (The details of these reactions are discussed in Section 5.) This third pigment has been found[6] recently in hen feathers (New Hampshire).

3.3. Model Reactions

The elucidation of the structures of these novel pigments, and the recognition of a new chromophore, was greatly assisted by studies[12, 15] on model compounds. Oxidation of a mixture of 4-methylcatechol (in place of dopa) and cysteine with alkaline ($NaHCO_3$) ferricyanide gave the unstable, yellow, quinone imine *(11)* which rapidly rearranged in stronger base (NaOH) to the isomeric lactam *(12)*. On treating *(11)* with acid the solution immediately became intensely violet and the product had the same chromophore as trichochromes E and F. Although this was gratifying the aryloxy group in these compounds is an undesirable complication, *(11)* being formed from one molecule of cysteine and *two* of 4-methylcatechol.



(11) *(12)*

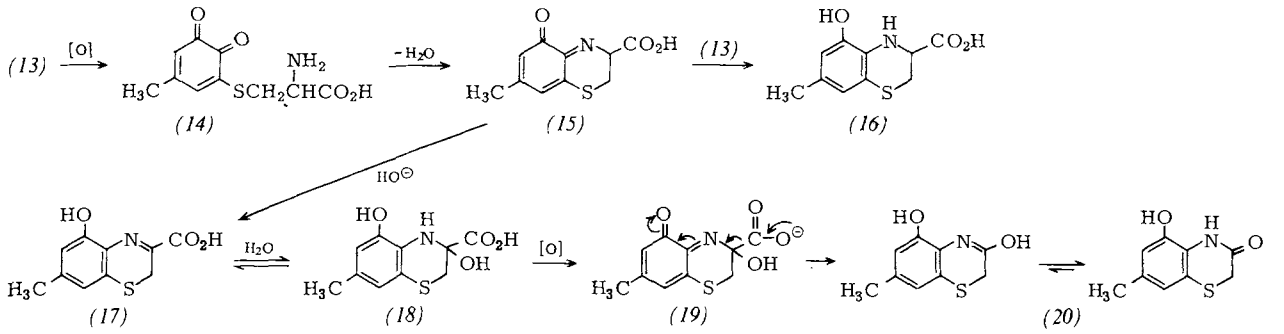


(13)

To avoid this kind of reaction the formation of the dihydrothiazine ring was then examined using 4-methyl-1,2-benzoquinone as the starting point. Reaction with cysteine hydrochloride gave the amino acid *(13)*, whose oxygenation in cold 0.1 M NaOH led to the lactam *(20)* ($\lambda_{max}^{HO^-}$ 322nm). By following this transformation spectrophotometrically a yellow precursor ($\lambda_{max}^{HO^-}$ 370nm) was detected in the early stages, and by stopping the reaction after 20 minutes the labile acid *(17)* could be isolated (after methylation).

Later[16], cyclization of *(13)* was effected under different conditions. When oxidized at pH 6.8 with mushroom polyphenol oxidase, or nonenzymically with a catalytic amount of oxygen, the amino acid *(16)* was rapidly formed in high yield. As only a small amount of oxygen is required for this reaction it appears that some *o*-quinone *(14)* is formed initially which then cyclizes with elimination of water to give the quinone imine *(15)*; this is then reduced to the product *(16)* by the starting compound *(13)*, more *o*-quinone being formed simultaneously, and so the cycle continues.

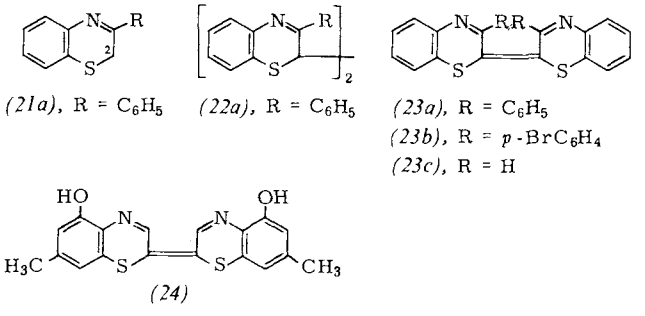
Scheme 1 outlines the sequence of reactions by which 1,4-benzothiazine derivatives are formed from the amino acid *(13)* (cf. refs.[15, 16]). It is of interest that the *o*-quinone *(14)* undergoes exclusive 1,2-addition and dehydration to form the quinone imine *(15)*, and the analogous compound from 4-



Scheme 1

methyl-1,2-benzoquinone and 2-aminoethanethiol behaves in the same way[17]; in neither case does the amino group cyclize by 1,4-addition to give an aminoquinone. The reaction in alkaline solution (Scheme 1) proceeds by base-catalyzed aromatization, hydration of the azomethine group in *(17)*, and oxidation of the resulting *o*-aminophenol *(18)* to *(19)* whence decarboxylation again results in aromatization and formation of the lactam *(20)*.

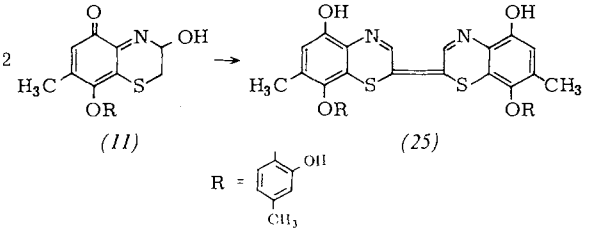
Regarding the conversion of these dihydrobenzothiazine derivatives into compounds of the trichochrome type, it is known that 2*H*-1,4-benzothiazines undergo oxidative dimerization very easily. This was first observed[18] with the 3-phenyl derivative *(21a)* which gave the dehydro dimer *(22a)* on heating with picric acid; the Italian group[19] has shown that this can be effected merely by oxygenation in acidified ethanol at room temperature. Chloranil effects further dehydrogenation and both *(21a)* and *(22a)* give *(23a)* in good yield in cold dioxane[12]. Similarly *(16)* affords *(24)* in a reaction involving oxidative decarboxylation[20].



(21a), R = C_6H_5 *(22a)*, R = C_6H_5 *(23a)*, R = C_6H_5
(23b), R = *p*-BrC_6H_4
(23c), R = H

(24)

The formation of synthetic $\Delta^{2,2'}$-bi(1,4-benzothiazines) in this way, presumably a radical coupling process, is relevant to the biogenesis of pigments of this type but the conversion



(11) *(25)*

of the quinone imine *(11)* into *(25)* in acid solution is a non-oxidative process which proceeds in the absence of oxygen.

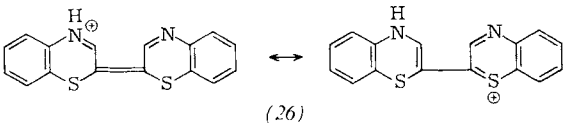
3.4. The Trichochrome Chromophore

The discovery of a new natural chromophore is a rare event. The trichochromes contain the conjugated system —S—C=C—C=N— and thus belong to the class of polymethine dyes, as do the betacyanin plant pigments. In acid solution protonation generates the mesomeric cation *(26)* resulting, in the case of *(9)*, *(10)*, and *(25)*, in a marked bathochromic shift of about 100 nm (see Table 1). This is reduced to *ca.* 70nm in the lactams *(7a)* and *(8a)*, while in trichochromes B *(7b)* and C *(8b)* the additional carboxyl group at C-3 so diminishes the basicity that protonation on the adjacent nitrogen does not normally occur. However, in acetic acid the thiazine nitrogen becomes more basic and protonation does occur with hydrogen chloride, the absorption maximum shifting to 550nm[12].

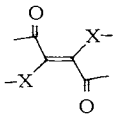
Table 1. Visible absorption of $\Delta^{2,2'}$-bi(1,4-benzothiazines).

	Cpd.	λ_{max} [nm] (log ε) in C_2H_5OH	in 0.1 M NaOH	in HCl [a]
(7b),	trichochrome B		454 (3.98)	450 sh [b]
(8b),	trichochrome C		452 (4.13)	460 sh [b]
(9),	trichochrome E		482	587 [c]
(10),	trichochrome F		482 (4.33)	587 (4.42) [c]
(7a)			462 (4.19)	525 (4.16) [c]
(8a)			458 (4.21)	525 (4.18) [c]
(23a)		466 (3.78)		594 (3.78) [d]
(23b)		478 (3.89)		625 (3.57) [d]
(25)		487 (4.34)		596 (4.45) [e]

[a] pH-dependent.
[b] In N HCl.
[c] In 2 N HCl.
[d] In C_2H_5OH/12 N HCl (84:16, v/v).
[e] In C_2H_5OH/12 N HCl (99:1, v/v).



(26)



(27)

When 3-aryl-2*H*-1,4-benzothiazines of type *(21)* are oxidized with chloranil both *cis* (red) and *trans* (yellow) forms are produced and for *(23b)* these have been isolated and subjected to X-ray analysis[21]. Both forms are stable in the solid state but in solution are interconvertible, even at room temperature, and consequently have very similar UV and visible absorption. Surprisingly, the *cis*-isomer is the more stable despite the crowding in the central part of the molecule.

The parent compound *(23c)* is not known[*]; it would be of interest to observe the *cis-trans* relationship in that case (large groups at C-3 and C-3' being absent) and moreover the *trans* form will be an indigoid dye as defined by *Lüttke*. It has been demonstrated by theory[22] and experiment[23] that the basic chromophore of these dyes can be represented by *(27)*, and the *trans* form of *(23c)* (and the trichochromes generally) contains the essential features, namely two donor and two acceptor groups arranged as in *(27)* to form a doubly cross-conjugated system.

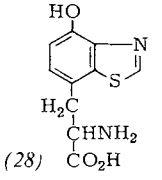
4. Gallophaeomelanins

These are the major pigments found in the feathers of New Hampshire hens *(Gallus gallus)*. They were separated[24] into four main fractions, gallophaeomelanins 1—4, by dialysis and chromatography on Sephadex, and so obtained as red-brown, amorphous, infusible, solids containing C, H, N, O, and S and soluble only in aqueous sodium hydroxide, formic acid, and acidic ethylene chlorohydrin. These fractions are mixtures of very similar macromolecules and are not chemical entities.

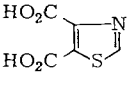
Gallophaeomelanin-1, the most abundant pigment, is protein-free and has an average molecular weight of *ca.* 2000. Gallophaeomelanins-2, -3, and -4 are chromoproteins, containing about 60% of a protein which is shown to differ from feather keratin by the absence of cystine from the sixteen amino acids obtained on hydrolysis. The phaeomelanins are generally intractable and cannot be usefully studied by the usual spectroscopic methods; the UV-visible spectra show no definite maxima while the IR and NMR spectra show only broad bands of little diagnostic value. The structural problem is thus similar to that presented by the eumelanins, and it was tackled in the same way by classical chemical degradation.

4.1. Gallophaeomelanin-1

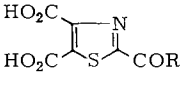
This pigment possesses carboxyl, primary amino, and phenolic groups. On alkali fusion[24] it gave a mixture of simple catechols and *o*-aminophenols, 4-amino-3-hydroxybenzoic acid being the most abundant, while oxidation[24] with hydrogen peroxide gave cysteic acid, and small amounts of glycine and aspartic acid. Significantly, pyrrole and indole derivatives, the characteristic degradation products of eumelanins, were absent, showing that phaeomelanins are not structural variants of eumelanins. Larger fragments, chiefly the amino acids *(2)* and *(4)* with smaller amounts of *(1)* and *(3)*, and the benzothiazole derivatives *(28)* and *(37)*, were obtained by heating the pigment in boiling hydriodic acid[24,25], while permanganate oxidation[26,27] yielded small amounts of the thiazole and pyridine acids *(29)*, *(30a)*, *(31a)*, and *(32)*. It was demonstrated that the acid *(29)* is derived from *(30a)* and that *(30a)* and *(31a)* arise from the amides *(30b)* and *(31b)* under the reaction conditions.



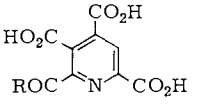
(28)



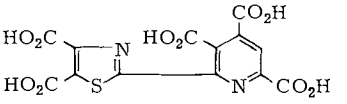
(29)



(30a), R = OH
(30b), R = NH_2



(31a), R = OH
(31b), R = NH_2



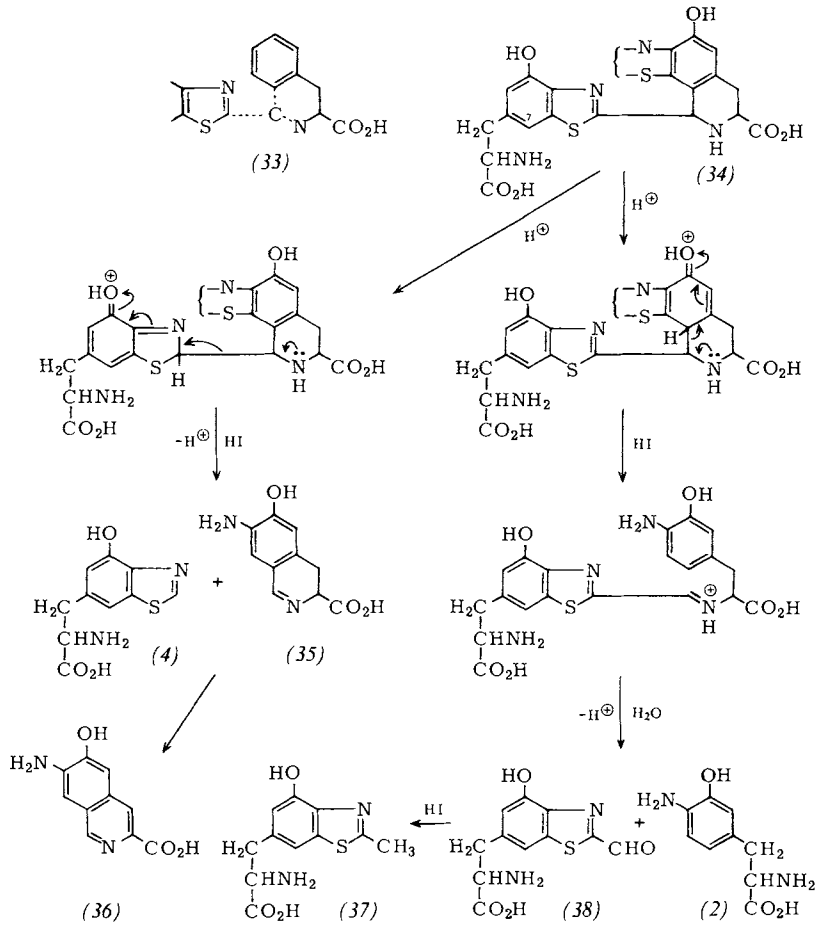
(32)

The key compound is *(32)*. While the thiazole part is clearly derived from a benzothiazole unit in the pigment, the origin of the pyridine moiety is less obvious. However, the likely origin of the gallophaeomelanins from dopa and cysteine suggested to *Minale et al.*[27] that a reduced pyridine ring might be formed in the course of biogenesis by cyclization of an alanyl side chain as indicated by *(33)*. If this is now extended to *(34)* (or the isomer with the side chain at C-7 in the benzothiazole unit) most of the degradation products can be explained (Scheme 2). The benzothiazoles *(4)*, *(28)*, and *(37)* could arise by reversed Mannich reactions, the methyl analog *(37)* being formed by reduction of *(38)* (not detected) since a model reaction showed that benzothiazole-2-carbaldehyde is rapidly reduced to 2-methylbenzothiazole in boiling hydriodic acid.

According to Scheme 2 one of the degradation products should be a 3,4-dihydroisoquinoline *(35)*. This was supported by further model experiments[28] and re-examination of the acid degradation products of gallophaeomelanin-1, by extensive chromatography, then led to the isolation[29] of three isoquinoline derivatives, including *(36)* (as its dimethyl derivative). Thus the existence of tetrahydroisoquinoline units of type *(34)* in gallophaeomelanin-1 seems very probable.

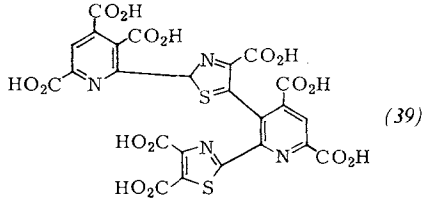
The largest degradation product derived from gallophaeomelanin-1 has not yet been mentioned. This was the polyacid *(39)*, obtained in 0.1% yield as its permethyl ester from a permanganate oxidation[27]. This compound must derive from a segment of the macromolecule containing three units such as those depicted in *(40)*, two of which are benzothiazole moieties. However, it is not certain whether all the benzothiazolylalanine *(4)* obtained on degradation comes from terminal residues as in *(40)*; the isomeric amino acid *(28)* must derive from isomeric benzothiazole units. The partial structure *(40)* represents the current view of the general structure of gallo-

[*] *Note added in proof:* This compound has now been synthesized (*G. Prota, E. Ponsiglione,* and *R. Ruggiero*, Tetrahedron, in press).

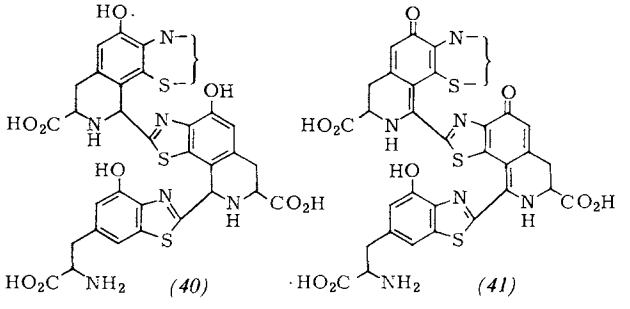


Scheme 2.

phaeomelanin-1 which of course is not a regular polymer. The degradation products include the benzothiazinone *(1)* and sulfoacetic acid[26] showing that some of the sulfur is



(39)



present in 1,4-thiazine rings; the substantial amount of cysteic acid (10%) obtained by hydrogen peroxide oxidation suggests the presence of uncyclized cysteinyl side chains. It is also evident that segments of the gallophaeomelanin-1 macromolecules must exist in a higher oxidation state in order to account for the visible absorption, and probably some of the phenolic rings in *(40)* actually exist in quinonoid form, possibly in conjugation [*(41)*].

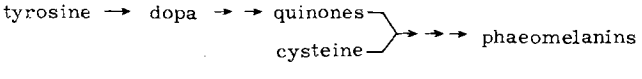
4.2. Other Gallophaeomelanins

Gallophaeomelanins-2, -3, and -4 gave the same degradation products as those obtained from gallophaeomelanin-1 and must have the same general structure, probably differing only in molecular weight and attachment to protein[24].

Fattorusso et al.[30] have also examined the red-brown pigments in the feathers of pheasants, partridges, pigeons and Rhode Island hens, in the hair of rabbits and goats, and in human "red" hair by the usual degradative procedures. They were all found to be gallophaeomelanins. The hair of certain brown goats and sheep contains only eumelanins, and the hair of roe deer eumelanins and gallophaeomelanins.

5. Biogenesis

The whole of the Neapolitan research has been guided by the hypothesis[10] that phaeomelanins are formed *in vivo* from tyrosine and cysteine by a deviation from the normal eumelanin pathway. Direct support for this idea was obtained



recently by a cytochemical study[31] of the formation of phaeomelanins in the feather papillae of New Hampshire chick embryos. This established that [3-^{14}C]-cysteine and [2-^{14}C]-tyrosine were specifically incorporated into pigment cells

whereas in the presence of a tyrosinase inhibitor the incorporation was negligible. This is consistent with earlier observations[32] of tyrosinase and dopa oxidase activity in eumelanic and phaeomelanic hair follicles and feather papillae.

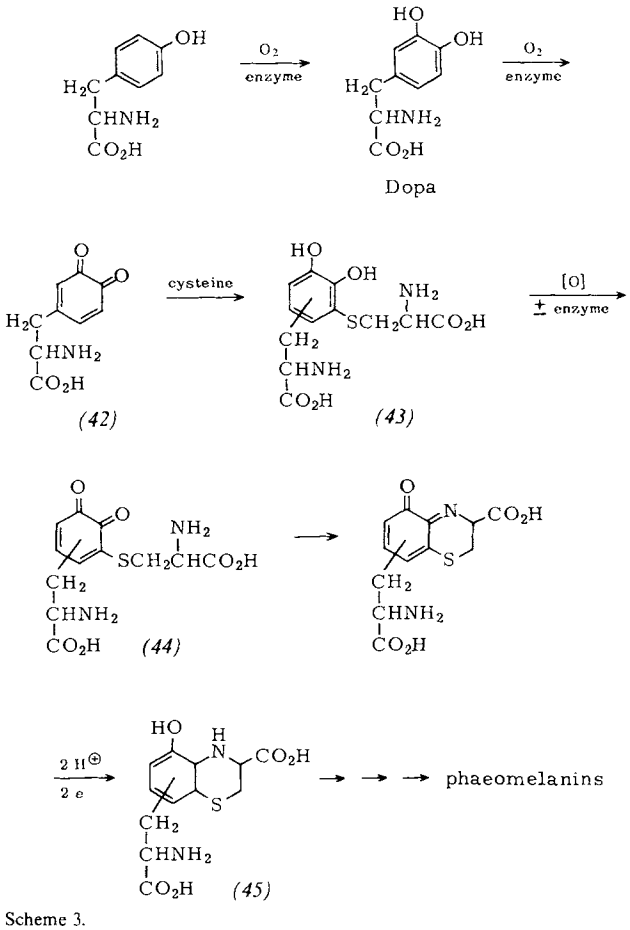
Subsequent study[33a] of the original enzymic oxidation of dopa and cysteine showed that the red-brown, amorphous end products were indistinguishable from gallophaeomelanin-1 and gave the same degradation products, predominately those derived from structural units originating in 5-*S*-cysteinyldopa. Trichochromes are not formed under these conditions; however if the oxidation mixture is acidified after a short time the violet pigments E and F are produced. These must derive from precursors formed at an early stage of phaeomelanogenesis. Examination of the oxidation products during the first 30 minutes of reaction, by automatic amino-acid analysis, revealed that 5- and 2-*S*-cysteinyldopa *(43)* were formed rapidly (the former in larger amount), and then disappeared. Hence the initial reaction is the oxidation of dopa to dopaquinone *(42)*, followed by 1,6-addition of cysteine[33b] which must be a fast reaction superseding the intramolecular addition which dopaquinone undergoes during eumelanin biogenesis. [In synthetic experiments[33] using cysteine ethyl ester and *N*-acetyldopaquinone ethyl ester both products of 1,6-addition can be isolated (after acetylation), the ratio 5-*S*-cysteinyl/2-*S*-cysteinyl derivative being 19:1.] Separate enzymic oxidations of 5- and 2-*S*-cysteinyldopa *(43)* then gave the expected phaeomelanins which afforded the same acid degradation products as before except that, as expected, the acids *(3)* and *(28)* were only obtained from "2-*S*-cysteinyldopa-phaeomelanin".

In further *in vitro* experiments *Prota et al.*[16] oxidized 5- and 2-*S*-cysteinyldopa, separately, with mushroom polyphenoloxidase at pH 6.8, following the reaction spectrophotometrically. It was found that within a few minutes the starting compounds were quantitatively converted into new products which were isolated and identified as the labile amino acids *(45)* by comparison with the model compound *(16)*. [The amino acids *(45)* were also formed non-enzymically from the cysteinyldopas *(43)* by oxygenation at pH 8.3.] Only a catalytic amount of oxygen is required in the enzymic oxidation to initiate formation of the *o*-quinone *(44)* after which the reaction proceeds spontaneously as in the model oxidation (Scheme 1).

Scheme 3[20] outlines the first phase of phaeomelanin biogenesis. Enzymic assistance is probably obligatory only for dopaquinone *(42)* formation, as in eumelanin biogenesis. It will be noted that the divergence from the eumelanin pathway follows immediately after dopaquinone formation, and it is the presence or absence of cysteine which determines whether melanocytes produce eumelanins and/or phaeomelanins.

A change in cysteine concentration may account for the color changes in the hair of agoutis, and indeed *Cleffmann*[34] has shown that an increase in the thiol content of agouti pigment cells precedes a change from the production of eumelanin to phaeomelanin. Interestingly, cysteinyldopa has been found recently in a malignant melanoma from a patient with "red" hair[35].

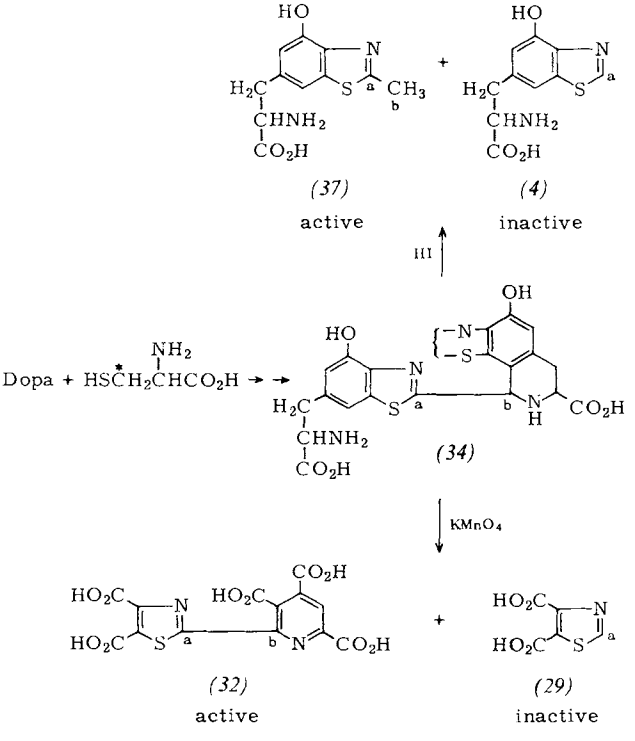
Very little is definitely known about the biogenesis of phaeomelanins beyond the dihydrobenzothiazine stage *(45)*. The red and violet pigments must surely be formed by oxidative dimerization, and while the details are uncertain it is clear from



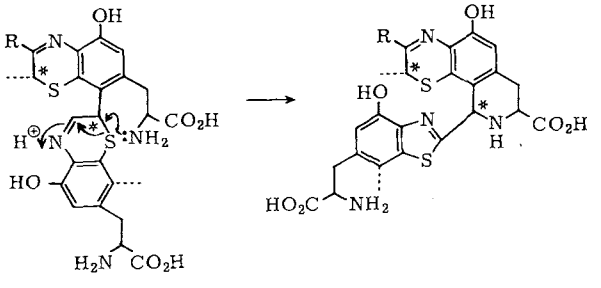
Scheme 3.

the model experiments that oxidative dimerization of the isomers *(45)* could lead to the formation of all the trichochromes, additional decarboxylation giving E and F, and oxidative decarboxylation producing B and C [cf. *(17)*→*(20)*].

Further information[36] concerning the biogenesis of the macromolecular pigments was obtained from an enzymic oxidation



of dopa and [3-^{14}C]-cysteine. Degradation of the resulting radioactive dopaphaeomelanin with hydriodic acid, and with alkaline permanganate, gave several products of which only *(32)* and *(37)* were active, the specific activity being almost the same as that of the labeled cysteine. Adopting partial structure *(34)* it can be seen that C_b arises from C-3 of cysteine, and C_a from C-2. As the precursor units of *(34)* are benzothiazines a ring contraction must occur in such a way that the sulfur atom of a thiazine ring becomes bonded to C-3 of that ring, C-2 becoming exocyclic. As benzothiazoles cannot be detected prior to pigment formation, it seems likely that polymerization occurs at the benzothiazine stage, followed by ring contraction. To account for this *Minale et al.*[36] suggest that benzothiazine units couple together at C-2 and C-8, and then undergo a transformation, shown in *(46)*, R = H or CO_2H, by which benzothiazole and tetrahydroisoquinoline systems are formed simultaneously. This is an ingenious idea. It assumes preliminary dehydrogenation of the dihydrothiazine ring (cf. Scheme 3) prior to ring contraction, which is reasonable. However, it would be interesting to know if 2*H*-benzothiazines can undergo oxidative coupling with phenols *in vitro*.



(46)

As noted earlier a minor product obtained by degradation of trichochrome C with hydriodic acid is the benzothiazole *(4)*, and this can also be obtained from the dihydrobenzothiazine *(1)* by boiling in hydrochloric acid[25]. This ring contraction is new.

I am grateful to the Laboratorio per la Chimica e Fisica delle Molecole di Interesse Biologico, C. N. R. Arco Felice, Naples, where this review was written, for generous hospitality, and to my Italian colleagues Professors E. Fattorusso, L. Minale, and G. Prota for information and criticism.

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[1] *R. A. Nicolaus:* Melanins. Hermann, Paris 1968.

[2] *L. E. Arnow*, Biochem. J. *32*, 1281 (1938).

[3] *H. C. Sorby*, J. Anthropol. Inst. *8*, 1 (1879).

[4] *S. Rothman* and *P. Flesch*, Proc. Soc. Exp. Biol. Med. *53*, 134 (1943); *P. Flesch* and *S. Rothman*, J. Invest. Dermatol. *6*, 257 (1945).

[5] *R. A. Nicolaus*, Chim. Ind. (Milano) *54*, 427 (1972).

[6] *G. Prota*, personal communication 1972.

[7] *N. A. Barnicot*, Nature *177*, 528 (1956).

[8] *P. Boldt*, Naturwissenschaften *51*, 265 (1964); *P. Boldt* and *E. Hermstedt*, Z. Naturforsch. *22b*, 718 (1967).

[9] *M. Nickerson*, Physiol. Zool. *19*, 66 (1946); *J. R. Smyth*, *J. W. Porter*, and *B. B. Bohren*, *ibid. 24*, 205 (1951); *E. M. Nicholls*, J. Invest. Dermatol. *53*, 302 (1969).

[10] *G. Prota* and *R. A. Nicolaus* in: Advances in Biology of Skin. *8*, 323 (1967).

[11] *G. Prota* and *R. A. Nicolaus*, Gazz. Chim. Ital. *97*, 665 (1967).

[12] *R. A. Nicolaus*, *G. Prota*, *C. Santacroce*, *G. Scherillo*, and *D. Sica*, Gazz. Chim. Ital. *99*, 323 (1969).

[13] *G. Prota*, *A. Suarato*, and *R. A. Nicolaus*, Experientia *27*, 1381 (1971).

[14] *G. Prota*, *G. Scherillo*, *O. Petrillo*, and *R. A. Nicolaus*, Gazz. Chim. Ital. *99*, 1193 (1969).

[15] *G. Prota*, *G. Scherillo*, *E. Napolano*, and *R. A. Nicolaus*, Gazz. Chim. Ital. *97*, 1451 (1967).

[16] *G. Prota*, *S. Crescenzi*, *G. Misuraca*, and *R. A. Nicolaus*, Experientia *26*, 1058 (1970).

[17] *G. Prota*, *O. Petrillo*, *C. Santacroce*, and *D. Sica*, J. Heterocycl. Chem. *7*, 555 (1970).

[18] *K. Fujii*, J. Pharm. Soc. Jap. *77*, 347 (1957).

[19] *D. Sica*, *C. Santacroce*, and *G. Prota*, J. Heterocycl. Chem. *7*, 1143 (1970).

[20] *G. Prota* in *V. Riley:* Pigmentation: Genesis and Biological Control. Appleton-Century-Crofts, New York 1972.

[21] *F. Giordano*, *L. Mazzarella*, *G. Prota*, *C. Santacroce*, and *D. Sica*, J. Chem. Soc. *C 1971*, 2610.

[22] *M. Klessinger* and *W. Lüttke*, Tetrahedron *19*, Suppl. 2, 315 (1963).

[23] *H. Hermann* and *W. Lüttke*, Chem. Ber. *101*, 1708 (1968); *E. Wille* and *W. Lüttke*, Angew. Chem. *83*, 853 (1971); Angew. Chem. internat. Edit. *10*, 803 (1971); *L. Fitjer* and *W. Lüttke*, Chem. Ber. *105*, 919 (1972).

[24] *L. Minale*, *E. Fattorusso*, *G. Cimino*, *S. De Stefano*, and *R. A. Nicolaus*, Gazz. Chim. Ital. *97*, 1636 (1967).

[25] *E. Fattorusso*, *L. Minale*, *S. De Stefano*, *G. Cimino*, and *R. A. Nicolaus*, Gazz. Chim. Ital. *98*, 1443 (1968).

[26] *E. Fattorusso*, *L. Minale*, *G. Cimino*, *S. De Stefano*, and *R. A. Nicolaus*, Gazz. Chim. Ital. *99*, 29 (1969).

[27] *L. Minale*, *E. Fattorusso*, *G. Cimino*, *S. De Stefano*, and *R. A. Nicolaus*, Gazz. Chim. Ital. *99*, 431 (1969).

[28] *L. Minale*, *E. Fattorusso*, *S. De Stefano*, *S. Magno*, *G. Cimino*, and *R. A. Nicolaus*, Gazz. Chim. Ital. *100*, 870 (1970).

[29] *E. Fattorusso*, *L. Minale*, *S. De Stefano*, and *R. A. Nicolaus*, Gazz. Chim. Ital. *100*, 880 (1970).

[30] *E. Fattorusso*, *L. Minale*, and *G. Sodano*, Gazz. Chim. Ital. *100*, 452 (1970).

[31] *G. Misuraca*, *R. A. Nicolaus*, *G. Prota*, and *G. Ghiara*, Experientia *25*, 920 (1969).

[32] *T. B. Fitzpatrick*, *P. Brunet*, and *A. Kukita* in *W. Montagna* and *R. A. Ellis:* The Biology of Hair Growth. Academic Press, New York 1958.

[33] a) *E. Fattorusso*, *L. Minale*, *S. De Stefano*, *G. Cimino*, and *R. A. Nicolaus*, Gazz. Chim. Ital. *99*, 969 (1969); b) *G. Prota*, *G. Scherillo*, and *R. A. Nicolaus*, *ibid. 98*, 495 (1968).

[34] *G. Cleffmann*, Exp. Cell Res. *35*, 590 (1964).

[35] *A. Björklund*, *B. Falck*, *S. Jacobsson*, *H. Rorsman*, *A.-M. Rosengren*, and *E. Rosengren*, Acta Dermato-Venereol., *52*, 357 (1972)

[36] *L. Minale*, *E. Fattorusso*, *S. De Stefano*, and *R. A. Nicolaus*, Gazz. Chim. Ital. *100*, 461 (1970).

Beech Lignin—Proposal of a Constitutional Scheme

By Horst Nimz[*]

The high molecular weight material lignin consists of phenylpropane units linked together by a variety of bond types. During the past eight years, two newly developed degradation procedures have permitted the first direct determinations of the nature of these bonds. The first procedure affords a very mild partial hydrolysis of benzyl ether bonds. Eleven dimeric, trimeric, and tetrameric degradation products were obtained in this way from spruce and beech lignin: they exhibited three different kinds of bonds between the C_9 structural units, and their structures have all been elucidated. In the second procedure, the most important kind of bond in lignin, *i.e.* the arylglycerol-β-aryl ether bond, can be subjected to directed cleavage under mild conditions after introduction of a suitable neighboring group. On application to beech lignin, 91% of the material was degraded giving monomeric to tetrameric phenols. Complete structural elucidation of the twenty dimeric phenols isolated and a knowledge of their relative yields and the yields of the other fractions obtained by gel filtration permitted a structural scheme to be set up for beech lignin in which the C_9 structural units are linked together by no less then ten different kinds of bonds. The structural scheme, which can be readily explained biogenetically, has the same elemental composition as natural beech lignin. Further support for the structural scheme comes from a comparison of the ^{13}C-NMR spectrum of natural beech lignin and a ^{13}C-NMR spectrum calculated for the proposed structure on the basis of about fifty lignin model substances.

1. Introduction

After cellulose, lignin is the second most abundant polymeric organic natural product. Being a major constituent of wood, large amounts of lignin are obtained as a by-product of cellulose manufacture. According to a recent estimate[1], the annual world production of pulp currently amounts to about 100 million tonnes, some 85% of this amount being produced by chemical processing of wood. Hence about 40 to 50 million tonnes of lignin are also produced in a single year. This is about twice the total global production of plastics. Since lignin has not yet found any large-scale industrial application, part of it is burnt to regain the chemicals used in wood processing or to satisfy the energy requirements of the pulp mills. A not inconsiderable amount is released as effluent and contributes to environmental pollution.

One of the main factors counteracting the utilization of lignin is to be found in its chemical structure, which in turn determines the properties of this high-molecular natural product. In spite of extensive lignin research[2-4] going back almost 140 years, considerable uncertainty surrounded the aromatic character of lignin long after the structure of other polymeric natural products such as cellulose had been established. The situation is characterized by an essay written in 1948 in which lignin is ascribed a purely aliphatic structure[5]. Although, in contrast to such a view, most lignin chemists had never doubted the aromatic nature of the structural units of lignin[6], unequivocal proof was not available until *Lange*[7] obtained microscopic evidence of absorption of monochromatic UV light by microtome sections in the 1940's and *Kratzl*[8] recorded IR difference spectra of lignin *in situ* in the early 1950's.

As early as 1910 *Klason*[9] expressed the opinion that lignin is a condensation product of coniferyl alcohol, hydroxyconiferyl alcohol, or coniferaldehyde, without being able to offer any proof. The chemical behavior of lignin on treatment with bromine[10], nitric acid[11], or mercury acetate[12], and in numerous other reactions, is also best rationalized by assuming the presence of phenylpropane structural units. This assumption could only be proved by hydrogenolytic lignin degradation with copper chromite catalysts to give propylcyclohexanes[13] and by "ethanolysis" leading to guaiacylpropane and syringylpropane derivatives[14]. However, the yields of these monomeric phenols were low.

Two and a half decades were to pass before the degradation of lignin to dimeric and oligomeric cleavage products bearing intact side chains was accomplished; this degradation will be considered in detail below. The principal difficulties encountered in partial lignin degradation came from condensation reactions forming new C—C bonds, and thus opposing degradation, which are promoted by the strong mineral acids or strong alkalies necessary for rupturing ether bonds. Avoidance of these secondary reactions by the use of very mild directed degradation conditions led to success. Meanwhile, the linkages of the C_9 units[*] in lignin had already been established in an indirect manner by *Freudenberg* and his school.

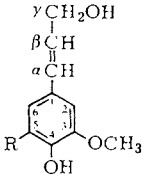
2. Biogenesis of Lignin

Most of our knowledge concerning the linkage of the C_9 units in lignin was deduced by *Freudenberg* and his co-workers from detailed biosynthetic studies performed in the 1950's and 1960's. The experimentally determined chemical and physical properties of lignin available in about 1950, its elemental composition, and results of oxidative dimerization of isoeugenol[15] suggested coniferyl alcohol *(1)* as a probable lignin precursor; its glucoside coniferin had already been detected in cambium by *Tiemann* and *Mendelsohn*[16] as long ago as

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[*] C_9 unit = phenylpropane skeleton; carbon atoms in substituents are not included.

1875. This initially hypothetical assumption was confirmed unequivocally in *Freudenberg*'s school by extensive experiments with labeled lignin precursors and by comparison of natural spruce lignin with the dehydrogenation polymer prepared *in vitro* from coniferyl alcohol[2]. The dimeric and oligomeric intermediates occurring on enzymatic dehydrogenation of coniferyl alcohol *in vitro* served as a basis for a structural scheme of spruce lignin[17]. A corresponding biogenetic path-

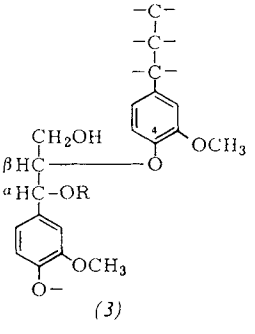


(1), R = H
(2), R = OCH_3

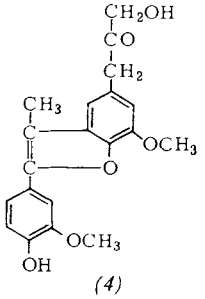
way was assumed for beech lignin, with the difference that synapyl alcohol *(2)* also acts as a precursor in addition to coniferyl alcohol[18].

3. Lignin Degradation by Mild Hydrolysis

The supplemented *Freudenberg* structural scheme[2] assumes nine different kinds of bonds between the C_9 units of spruce lignin, the commonest being the β-aryl ether bond shown in *(3)* which is designated the β-O-4 bond in lignin chemistry[3]. This bond explains the formation of monomeric arylpropanones (Hibbert ketones) on acidolysis[19] of lignin. In 1964 *Lundquist*[20] was able to isolate phenylcoumarone (phenyl-1-benzofuran) *(4)* as the first dimeric degradation product of lignin from the acidolytic products of milled wood lignin (MWL); its formation can also be explained by cleavage of a β-O-4 bond. However, model studies have shown[21,22] that under the acidolytic conditions required for rupture of the β-O-4 bond lignin is prone to undergo condensation reactions leading to new C—C bonds.



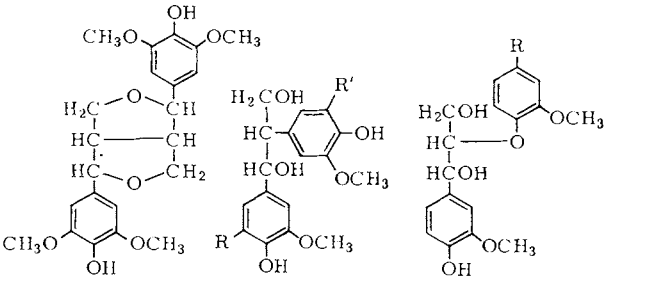
(3)



(4)

Very mild hydrolysis conditions under which no condensation takes place should suffice to cleave acyclic α-O-4 bonds, also shown in formula *(3)* (R = aryl), which account for 8 to 10% of all bonds in spruce lignin[23,24]. Hydrolytic rupture of these benzyl ether bonds would hence lead to partial degradation of lignin and to small quantities of low-molecular cleavage products.

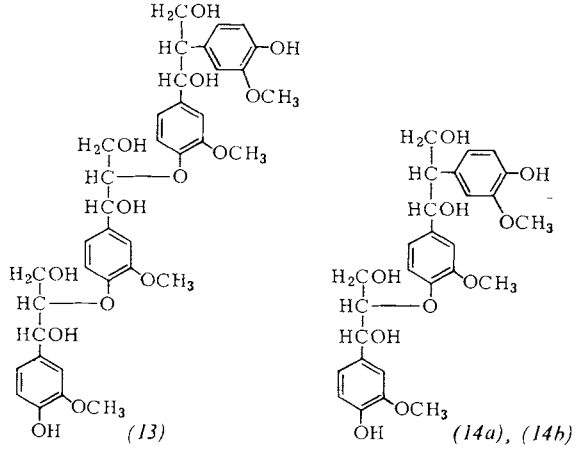
These concepts were successfully implemented by percolation of finely ground, pre-extracted wood with water at 100 °C. After several weeks' percolation, beech wood *(Fagus silvatica)* loses about 40% of its lignin component, while only 20% of the lignin present in spruce wood *(Picea excelsa)* goes into solution under the same conditions[25-27]. Apart from hemicelluloses and high-molecular phenolic components arising from lignin, the aqueous extract contains low-molecular cleavage products of lignin which can be isolated by countercurrent distribution, column chromatography, and recycling chromatography. In all, the structures of eight dimers [*(5)* to *(12)*], two diastereoisomeric trimers [*(14a)*, *(14b)*], and one tetrameric phenol [*(13)*] (Fig. 1) could be established[25-29].



(5)

(6), R = R' = H
(7), R = H, R' = OCH_3
(8), R = R' = OCH_3

(9), R = CH=CH-CH_2OH
(10), R = CH=CH-CHO
(11), R = $(CHOH)_2$-CH_2OH
(12), R = CHO



(13)

(14a), *(14b)*

Fig. 1. Dimeric, trimeric, and tetrameric phenols obtained by mild hydrolysis of beech or spruce lignin.

Since the degradation products in Figure 1 all arise under conditions leading to no secondary reactions they furnish information about the linkage of the C_9 units in lignin. Isolation of the dilignols[*] *(9)* to *(12)* having β-O-4 bonds constitutes the first direct proof of the occurrence of this type of bond in lignin; the β-O-4 bond had already been assumed to represent the most important bond type in spruce lignin on the basis of biosynthetic studies[2]. The same applies to syringaresinol *(5)*.

In contrast, the three dilignols *(6)* to *(8)* evidence a type of bond (β-1 bond) not included by *Freudenberg* in his original structural postulate[17] since the corresponding dilignol was not detected among the dehydrogenation products of coniferyl alcohol. It was subsequently detected in very low concentrations[30]. The results of lignin degradation with thioacetic acid (see Section 4) nevertheless indicate that the β-1 linkage is one of the principal bond types in lignin. This apparent discrepancy is explained by the slight tendency of coniferyl

[*] Use of the term lignol for the low molecular degradation products of lignin was established by *Freudenberg* [17].

alcohol to undergo coupling at C-1 with loss of the propenyl group. Such linkage only becomes significant when a saturated side chain bearing an α hydroxy group is present[27,31]. A high concentration of preformed oligomers and low coniferyl alcohol concentration are therefore essential conditions for β-1 coupling: these conditions are satisfied in plants.

4. Lignin Degradation with Thioacetic Acid

Since only partial degradation of lignin is accomplished under mild hydrolysis conditions (see Section 3), the yields of degradation products (see Fig. 1) provide no information about the relative proportions of the three types of bonds found in lignin. Moreover, it can hardly be expected that all types of bonds present will be detected. A structural scheme will therefore require complete degradation of lignin to low molecular weight products amenable to structural elucidation. The structure proposed by *Freudenberg* would indicate that extensive degradation of lignin can be accomplished only if the β-O-4 bonds can be cleaved without attendant condensation reactions. This end has been achieved in the following manner[32] (Fig. 2).

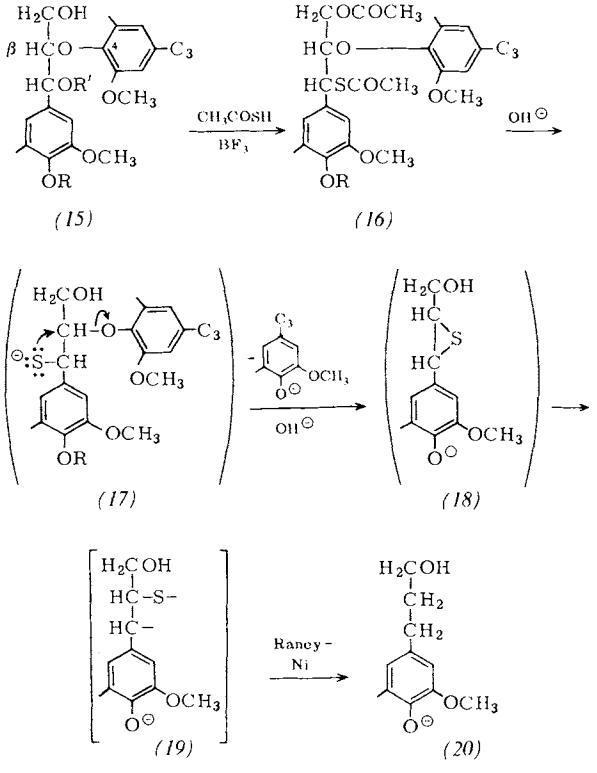


Fig. 2. Cleavage of the β-O-4 bond on degradation of lignin with thioacetic acid.

Dimeric lignin model substances *(15)* containing a β-O-4 bond give high yields of *S*-benzyl thioacetates *(16)*[33] on treatment with thioacetic acid and catalytic amounts of boron trifluoride at 20 °C. Nonbenzylic hydroxy groups are converted into *O*-acetates. Presumably, benzyl cations are formed initially by the action of boron trifluoride and then react immediately with the nucleophilic thioacetic acid or its anion. Hydrolysis of the thioacetates with 2 N NaOH at 60 °C yields intermediate benzyl thiolate ions *(17)* in which the nucleophilic sulfur attacks the neighboring β-carbon atom with displacement of the phenolate ion[34]. The resulting thiirane *(18)* polymerizes to thioethers *(19)*, some loss of γ-carbon atom as formaldehyde sometimes also occurring. Dimeric model substances give varying yields of dithianes[33]. The sulfur in the thioethers *(19)* can be replaced by hydrogen with the aid of Raney nickel[35].

The result of this degradation is a specific cleavage of β-O-4 bonds in lignin under mild conditions precluding secondary reactions. Oxygen functions attached to C-α and C-β are simultaneously replaced by hydrogen. Moreover, since the chirality centers at these carbon atoms are eliminated, the final degradation products are sterically homogeneous compounds, most of which crystallize or can be readily purified by chromatography. This point is of some importance in view of the complicated degradation mixtures obtained from lignin.

The starting material used for lignin degradation was finely ground wood that had been pre-extracted with acetone/water (9:1) and dried over P_2O_5. Successive action of thioacetic acid-boron trifluoride and 2 N NaOH on this material resulted in complete dissolution of the lignin and hemicelluloses of both beech wood *(Fagus silvatica)*[36] and spruce wood *(Picea excelsa)*[32]. Treatment of the alkaline solution with Raney nickel converted the lignin product fraction into a mixture of phenolic degradation products completely soluble in ethyl acetate; the hemicelluloses could be removed by extraction with water. The lignin degradation products were then separated into five fractions (A—E) of varying molecular size by gel permeation on Sephadex LH-20. The components of these fractions are shown in Table 1.

As seen from Table 1, 91% of beech lignin is degraded to mono- to tetralignols. The molecular weight distribution of the oligomeric component (fraction A)[36] shows it to consist of molecules having a molecular weight below 2000 to the extent of 99%. Spruce lignin, on the other hand, gives only 77% of monomeric to tetrameric phenols (B—E)[32].

Chromatography of the monomeric fraction (E) from beech lignin gave 49% of 2,6-dimethoxy-4-propylphenol, 14% of 2-methoxy-4-propylphenol, and 12% of three further identified monolignols. Since the hydroxy groups on the side chains of the C_9 units are largely removed during degradation, the proportion of isolated homogeneous monolignols corresponds to about 40% of the lignin.

In addition, each one of the twenty dilignols present in detectable amounts in fraction D could be isolated and its structure

Table 1. Yields of fractions A—E obtained from 100 g of beech wood (for details see text).

Fraction	A oligomeric	B tetrameric	C trimeric	D dimeric	E monomeric
Yield [g]	2.91	1.71	3.49	8.03	15.94
Percentage of total yield	9.1	5.3	10.9	25.0	49.7

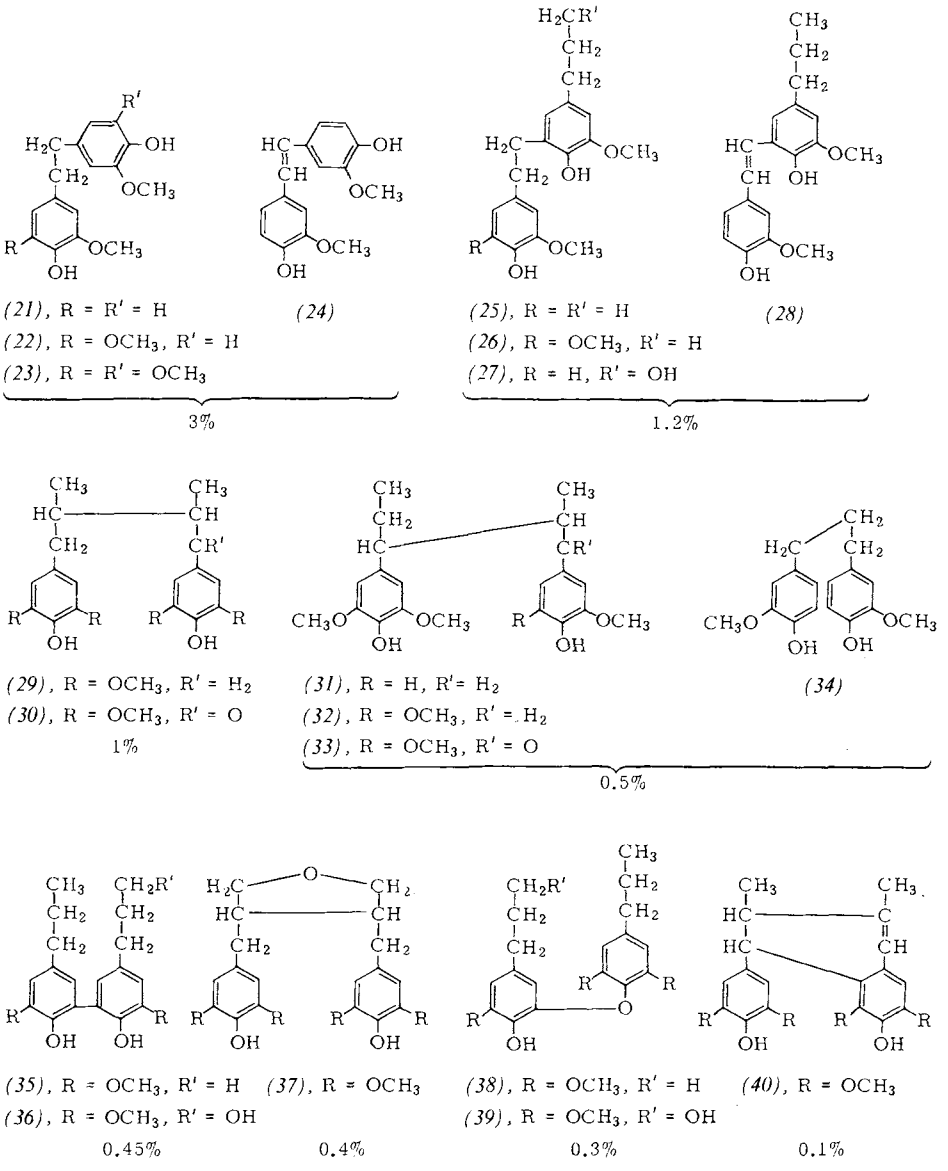


Fig. 3. Dilignols obtained on degradation of beech lignin with thioacetic acid. The yields of analytically pure products (mean values of several determinations) given under the formulas are based on lignin.

determined[37]. They are collected as structural types in order of decreasing yield in Figure 3. Although losses predictably occur on chromatographic isolation of the dilignols, their relative yields should not change significantly.

are partly removed as formaldehyde or reduced to methyl groups. The dilignols shown in Figure 3, which contain no such ether linkages, can therefore be unequivocally ascribed to dimeric structural units in lignin. Moreover, the proportion

Table 2. Proportions of various bond types in beech lignin.

Bond type	Dilignols	Proportions [%]
Acyclic α- and β-ethers	—	65
β-1 bonds (1,2-diarylpropane units)	(21)—(24)	15
β-5 bonds (phenylcoumaran units)	(25)—(28)	6
β-β bonds (syringaresinol and pinoresinol units)	(29), (30)	5
α-β bonds	(31)—(34)	2.5
5-5 bonds (biphenyl units)	(35), (36)	2.3
β-β bonds in dibenzyltetrahydrofuran units	(37)	2
5-O-4 bonds (diphenyl ether units)	(38), (39)	1.5
β-β and α-6 bonds (tetralin units)	(40)	0.5

5. Structural Scheme of Beech Lignin

Model experiments[33] show that thioacetic acid cleaves only ether linkages at C-α and C-β, while γ-hydroxymethyl groups

of those bonds which are cleaved during thioacetic acid degradation of lignin can be calculated from the yields of monomeric to oligomeric phenols listed in Table 1. If lignin were to have a chain-like unbranched structure then the proportion

of cleaved bonds would amount to 67%[*]. Since lignin contains both crosslinked, threefold bonded C_9 units and terminal C_9 units, the latter being presumed to predominate in beech lignin, about 65% of the bonds in beech lignin should be cleaved on thioacetic acid degradation. Hence it follows that this number can be equated to the proportion of α- and β-ether linkages in beech lignin. If it is now assumed that the uncleaved bonds (in all 35%) in lignin occur in the same ratio as that deduced from the yields of dilignols (Fig. 3) then we can estimate the proportions for ten types of bonds between the phenylpropane units of beech lignin (Table 2).

On the basis of the proportions of the various bonds listed in Table 2, a structural scheme was set up for beech lignin (Fig. 4).

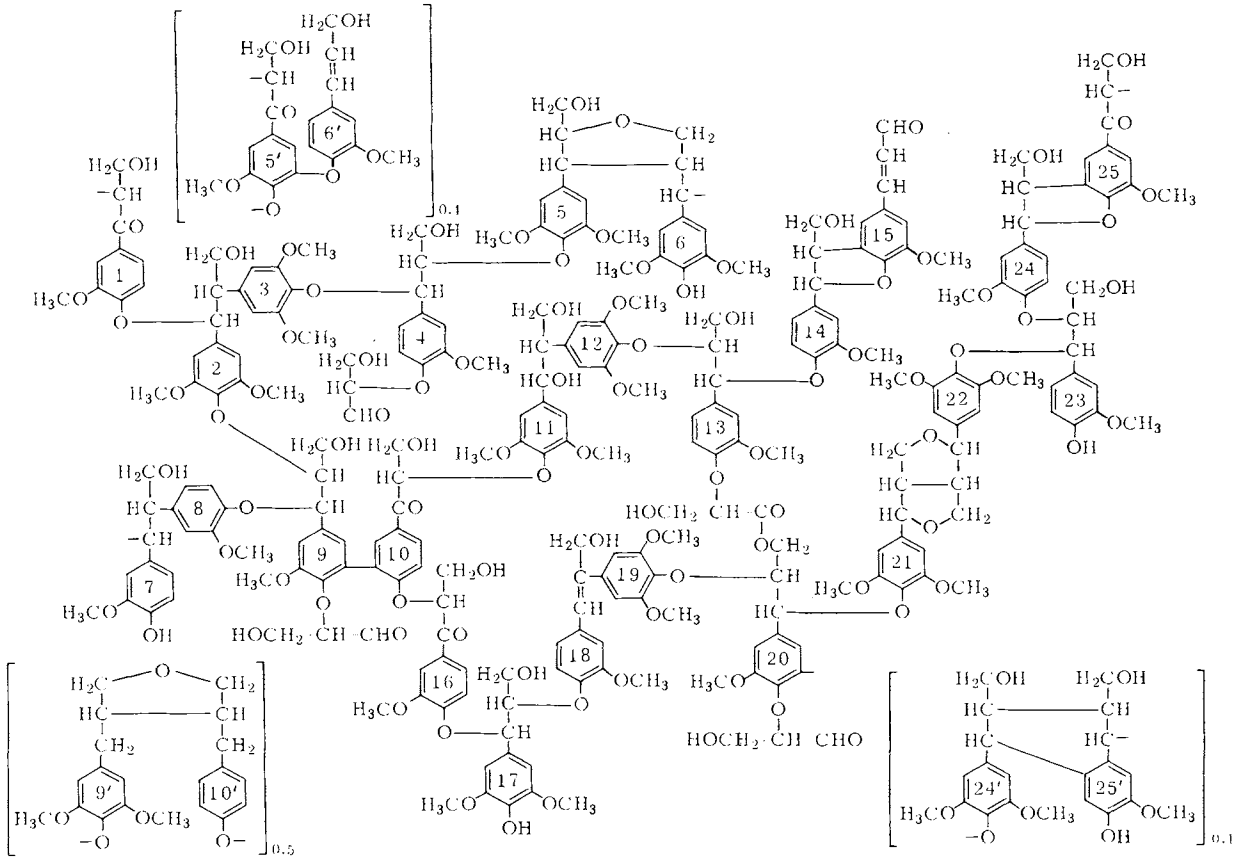


Fig. 4. Proposed structure of beech lignin. The C_9 units are ascribed consecutive numbers. For details see text.

The proposed scheme consists of 25 C_9 units of which six (5/6, 9/10, 24/25) can to some extent be replaced by the dilignol units enclosed in brackets. The scheme shows a representative section from a beech lignin molecule some ten or twenty times larger in which the ten different bond types are randomly distributed. The glyceraldehyde or glyceric acid groups linked by a β-ether bond to the C_9 units 4, 9, 13, and 20 which are not detected on degradation are clearly evidenced by the occurrence of the β-1 dilignol units 2/3, 7/8, 11/12, and 18/19, during whose formation they arise by release of a C_3 side chain[27, 31]. These glyceraldehyde β-ethers could be detected in spruce lignin[38].

The composition depicted in Figure 4 (molecular formula $C_{259}H_{281}O_{95}$) can be rationalized in terms of oxidative coupling of a mixture of fourteen molecules of coniferyl alcohol *(1)*, ten molecules of synapyl alcohol *(2)*, and one molecule of *p*-coumaryl alcohol [*(1)* with H in place of OCH_3], 59 hydrogens being removed (= 2.36 per C_9 unit) and 11 molecules of water added.

Division of the molecular formula by 25 and elimination of the methoxy groups yields

$$C_{10.36}H_{11.24}O_{3.80} = C_9H_{7.16}O_{2.44}(OCH_3)_{1.36}$$

as the mean composition of the C_9 unit in the structural scheme. The deviation from the mean composition of the C_9 unit in natural beech lignin[18]

$$C_9H_{7.10}O_{2.41}(OCH_3)_{1.36}$$

calculated from elemental analysis amounts to only 3% of water and thus lies within the limits of accuracy.

6. Physical Methods of Structural Elucidation

6.1. UV Spectra and Ionization Δε Curves

The UV spectrum[39] of beech MWL differs only slightly from those of other deciduous lignins. A slight shift of the

[*] Since only α- and β-ether linkages involving the C_3 side chains of C_9 units in lignin are cleaved during degradation, a *ca.* 50% relative proportion of monomeric phenols (fraction E, Table 1) means that half of all C_9 units in beech lignin are linked together exclusively *via* ether bonds of this type. A further 25% of the C_9 units obtained as dimers (D) must each be half involved in such bonds. Addition of 1/3 × 11% and 1/4 × 5% for the proportions of trimers (C) and tetramers (B) yields about 67% of ether bonds [36].

maximum at 280nm to 277nm compared with coniferous lignins can be ascribed to the effect of syringyl groups (3,5-dimethoxy-4-hydroxyphenyl) which are absent from coniferous lignins.

The ionization $\Delta\varepsilon$ curve[39] (difference between the extinctions in alkaline and neutral solution) of beech lignin exhibits three maxima: one flat maximum ranging over 320 to 400nm can be assigned to phenolic C_9 units having conjugated carbonyl and vinyl groups in their side chains or to biphenyl units[40] whose absorption regions overlap. Two further maxima at 253 and 300 are ascribed to phenolic units in non-conjugated systems. Additional difference spectra can be obtained after reduction with $NaBH_4$ (reduction $\Delta\varepsilon$ curves) or after catalytic hydrogenation (hydrogenation $\Delta\varepsilon$ curves)[41].

Šutý and *Golis*[42] have recently calculated the values for phenolic and non-phenolic cinnamaldehyde, cinnamyl alcohol, α-keto, biphenyl, and non-conjugated units in beech lignin from the difference spectra of hydrogenated and sulfonated beech MWL. The most serious difference from the structural scheme shown in Figure 4 lies in the number of biphenyl (5-5) bonds, reported as 20 per 100 C_9 units (cf. Table 2: 2.5%). Since no details are given concerning the preparation of the ligninsulfonic acid used, we cannot engage in a discussion of the origin of this discrepancy. In contrast, the value calculated by *Šutý* and *Golis* from the difference spectrum obtained on acidolysis for phenylcoumaran (phenyl-2,3-dihydro-1-benzofuran) units (7%) agrees well with our value (6%, Table 2). It should be pointed out that the method of calculating structural units in beech lignin from UV difference spectra embodies a number of uncertainties, owing to the multitude of chromophoric systems in deciduous lignins, and can easily lead to false conclusions.

6.2. IR Spectra

The rather structureless IR spectrum[18] of beech lignin possesses two bands of medium intensity in the carbonyl range at 1667 and 1750 cm^{-1} which are not sharply distinguished from each other. The former can be assigned to α-carbonyl and cinnamaldehyde groups of which there are 4.8 (1.9% of all C atoms) in the structural scheme. The band at 1750 cm^{-1} showing a spread to low wave numbers can be ascribed to the three aliphatic aldehyde groups and the one aliphatic ester group of the Scheme (Fig. 4). The ^{13}C spectrum (see Section 6.4) of beech MWL indicates the presence of acetyl groups, which are probably bound to hemicelluloses[43] from which complete separation of beech lignin is extremely difficult. For this reason we boiled beech MWL with 0.2% sulfuric acid for 30min prior to elemental analysis.

6.3. ^{1}H-NMR Spectra

High resolution ^{1}H-NMR spectroscopy has afforded valuable services in structural elucidation of low-molecular weight degradation products[29, 37, 44]. It must be borne in mind, however, on evaluation of lignin spectra[44–46] that the high viscosity of the sample solutions and the very limited mobility of the high-molecular crosslinked lignin molecules can lead to line broadening and possibly to a drop in signal intensity. Line broadening and signal overlapping also arise from spin-spin coupling, chirality centers, steric interactions, and owing to the exceptional structural complexity of lignin.

Even in regions where no overlapping would be expected between the signals of different kinds of protons, the unfavorable intensity ratio of the signals effectively precludes quantitative determination of particular kinds of protons. This applies to the α protons in phenylcoumaran units (H-α in the C_9 units 14 and 24 in Fig. 4) which absorb in a region ($\delta = 5.18$ to 5.74 ppm) which should be devoid of any other absorptions due to lignin protons. The proportion of these protons was calculated as 3.18 per 100 C_9 units from the relative intensity of this region of the beech lignin NMR spectrum[42]. However, in view of the fact that 100 C_9 units contain about 1100 protons and the "molecular weight" of these 100 C_9 units is 19656.4, the performance of the method is clearly overtaxed.

In contrast, the intensity ratios of the strongest signals in the spectrum should permit semiquantitative determination of the ratio of aromatic to methoxy protons[45, 46]. Aliphatically and aromatically bonded acetoxy groups can be included in this comparison if observations are performed on acetylated lignin. The relative intensities of the specific absorption regions of these kinds of protons are shown in Table 3.

Table 3. Intensity ratio of the most important signals in the ^{1}H-NMR spectrum of acetylated beech lignin (chemical shifts in ppm relative to TMS).

Type of proton	δ	I_{rel}	No. of groups
Aromatic and α-vinylic	6.3–7.6	2.5	1.1
Methoxy	3.5–4.0	4.1	1.36
Aromatically bound acetoxy	2.2–2.4	0.9	0.3
Aliphatically bound acetoxy	1.8–2.2	4.6	1.53

From Table 3, we calculate 2.5 aromatic and α-vinylic protons, and 0.3 phenolic and 1.53 alcoholic hydroxy groups for each C_9 unit in beech lignin (or per 1.36 methoxy group). In contrast, the structural scheme (Fig. 4) contains 2.55 aromatic and α-vinylic protons, 0.15 phenolic and 0.94 alcoholic hydroxy groups per C_9 unit. The deviations of the hydroxy groups result on the one hand from the carbohydrate components of beech MWL, which can be detected by thermofractography[47], and on the other hand from the fact that only about a third of the lignin is obtained from the wood as soluble MWL by *Björkman*'s method[48]. The insoluble portion remaining in the wood is more extensively crosslinked[49] and should contain fewer free phenolic groups[*]. Moreover, the benzyl aryl ether bonds (0.28 per C_9 unit) assumed in the structural scheme will undergo preferred cleavage as the weakest points of linkage between C_9 units during mechanical lignin degradation by vibrational grinding to prepare MWL, thus also releasing free phenolic groups.

6.4. ^{13}C-NMR Spectra

Compared with ^{1}H-NMR spectroscopy, PFT ^{13}C-NMR spectroscopy[50] has the advantage of greatly superior resolution

[*] *Note added in proof* (April 17, 1974): *W. Schweers* and *O. Faix* [55] recently found that a synthetic "hardwood lignin" (mixed DHP) obtained on dehydrogenating a mixture of coniferyl and sinapyl alcohols contains fewer free phenolic groups than a synthetic "softwood lignin" obtained from coniferyl alcohol alone. The low content of free phenolic groups in beech lignin is evidenced by the intensities of the signals for the C-3 and C-5 atoms in phenolic (148.5 ppm) and etherified (154.5 ppm) syringyl units in the ^{13}C-NMR spectrum (cf. Fig. 5a and Table 4).

owing to a twenty-fold field expansion and spin-spin decoupling. Figure 5a depicts the proton noise decoupled ^{13}C-NMR spectrum of beech MWL.

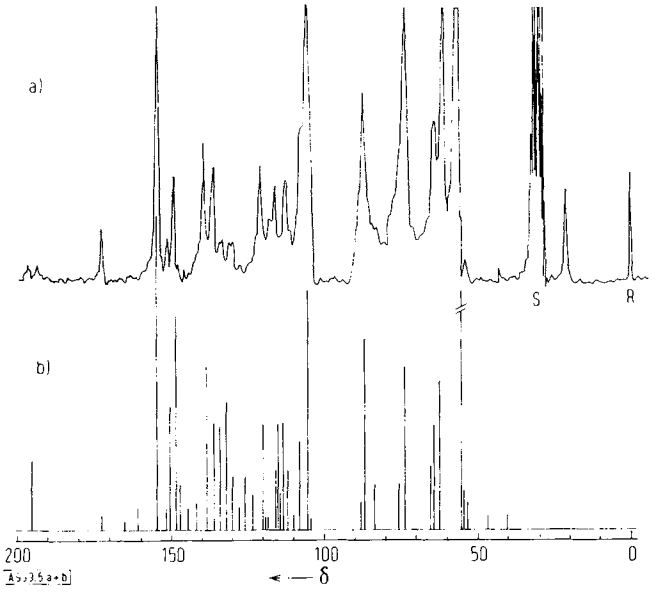


Fig. 5. a) 25.2 MHz PFT ^{13}C-NMR spectrum of a 20% solution of beech lignin (MWL) in hexadeuterioacetone/D_2O (9:1), recorded with a Varian XL 100-15 spectrometer. δ values in ppm downfield from TMS. b) Calculated ^{13}C-NMR spectrum of the structural scheme (Fig. 4). For details see text. S = acetone, R = TMS.

The chemical shifts of nearly all the carbon atoms occurring in the proposed structure (Fig. 4) could be determined from the ^{13}C-NMR spectra of over fifty lignin model substances[51]. They are compared with the δ values from the lignin spectrum (Fig. 5a) in Table 4.

The only carbon atoms not included in Table 4 are the carbonyl carbons of the three etherified glyceraldehyde (C_3) units on C_9 units nos. 4, 9, and 20, and the α, β, and γ carbons of C_9 unit no. 5 of the structural scheme (Fig. 4), for which no suitable comparison samples have yet become available. Furthermore, no distinction is made in Table 4 between the α carbon atoms in benzyl ethers and in non-etherified benzyl alcohols.

On the basis of the δ values (Table 4) determined from the ^{13}C-NMR spectra of model substances, a "calculated spectrum" (Fig. 5b) can be drawn for the structural scheme (Fig. 4). The signals are drawn as lines whose heights represent the number of corresponding carbon atoms. Since the nuclear Overhauser effect and the spin lattice relaxation times (T_1) are neglected, the heights of the lines in the "calculated spectrum" (Fig. 5b) can only be qualitatively compared with the intensities of the signals in the lignin spectrum (Fig. 5a). However, the chemical shifts in the two spectra should not differ significantly. That this requirement is satisfied, apart from a few explicable exceptions, is apparent from a comparison of the two spectra and of the δ values given in Table 4.

The weak signal at 192.7 ppm observed only in the lignin spectrum (Fig. 5a) can be assigned to an α-aldehyde group (*e.g.* in vanillin) such as is found in the dilignol *(12)* (Fig. 1) obtained on mild hydrolysis. It was not included in the structural scheme (Fig. 4), however, since it can only be explained biogenetically by assuming the occurrence of an additional monomeric lignin precursor. No decision could be reached whether glyceraldehyde groups of the proposed structure might possibly be responsible for this signal. The

Table 4. Comparison of the ^{13}C chemical shifts (δ) of beech lignin with those predicted for the proposed structure (Fig. 4). The numbers accompanying the assignment refer to the C_9 units of the structural scheme.

Lignin [ppm] *I* [a]	Values calculated for the proposed structure [ppm]	C_n [b]	Assignment
195.2 w	195	4.8	C-α in 1,5',10,16,25; C-γ in 15
192.7 w			(C-α in vanillin)
171.8 m	172	1	O—C=O in aliphatic ester between 13 and 20
	165	0.5	C-4 in 10
162.0 vw	161	1.4	C-4 in 10'; C-5 in 25
154.5 vs	154.5	20.3	C-3 + C-5 in 2,3,5,5',9',11,12,19,21,22,24'; C-4 in 1,16; C-α in 15
152.9 vw	152	1.4	C-4 in 6',18
150.6 w	150.4	7.9	C-4 in 4,8,13,14,20,24; C-3 in 1,16
148.5 m	148.5	13.7	C-3 in 4,6',7,8,9,13,14,18,20,23,24; C-3 + C-5 in 6,17; C-4 in 9
146.6 w	147	3.1	C-4 in 7,15,23,25'
144.8 vw	145	1.4	C-3 in 25,25'; C-4 in 5'
	142	1.9	C-4 in 19,25
138.7 m	138.5	12.5	C-4 in 2,3,5,11,12,9',21,22,24'; C-1 in 2,11,21,22,24',25'; C-3 in 15; C-6 in 25'
136.0 m	136	7.0	C-1 in 4,9,13,14,20,24; C-4 in 6,17
133.6 w	134	7.7	C-1 in 3,5,6,7,9',12,17,19,23
132.7 w	132	7.9	C-1 in 1,6',8,10,10',18; C-β in 15,18; C-2 in 10; C-α in 18
130.2 w	130	3.8	C-1 in 15,16,5'; C-5 in 15; C-α in 6'
129.0 w	128	2.0	C-5 in 9; C-2 + C-6 in 10'; C-6 in 10
126.7 vw	126.3	3.8	C-6 in 1,16; C-1 in 25; C-3 in 10; C-β in 6'
	123	2.4	C-6 in 6',8,18
120.1 m	120	6.9	C-6 in 4,7,13,14,20,23,24
	119	1	C-6 in 9; C-5 in 10
117.5 w	118	1	C-6 in 15
115.6 m	116	4	C-5 in 7,23; C-2 in 8; C-3 + C-5 in 10'
	115	6.9	C-5 in 4,13,14,18,20,24; C-2 in 16
113.8 vw	114	2.4	C-5 in 8,6'; C-2 in 1
	113	7	C-2 in 4,13,14,20,24; C-5 in 1,16,25'
112.0 m	111.6	4	C-2 in 6',7,9,18,23,25'
	110	1	C-2 in 15
107.1 m	108	5.9	C-2 + C-6 in 3,5',12,24'; C-6 in 25
105.1 vs	105	15.4	C-2 + C-6 in 2,5,6,9',11,17,19,21,22
	104	0.9	C-2 in 25
88.1 vw	88	1.9	C-α in 14,24
86.8 s	87	12.2	C-β in 4,9,13,17,20,23; C-α in 6,21,22,25'; C-β in C_3 units on 4,9,13,20
85.8 vw			
81–84 w	83	3.9	C-β in 1,5',10,16,25
75 w	75	3	C-α in 2,7,11
73.3 vs	73	9.2	C-α in 4,9,13,17,20,23; C-γ in 6,9',10',21,22
	64.8	5.1	C-γ in 2,7,11,14,24,24',25'
63.8 m	63.8	8.3	C-γ in 1,5',6',10,16,18,25; C-β in 2,7,11
61.3 vs	61.8	9.5	C-γ in 4,9,13,17,20,23; C-γ in C_3 units on 4,9,13,20
56.3 vs	56.3	33.8	OCH_3; C-α in 24'
54.5 w	55	2.7	C-β in 6,21,22,25'
	54	2	C-β in 14,24,24'
52.3 vw			
46.8 vw	47	1	C-β in 9',10'
	40	1	C-α in 9',10'
20.8 m			(CH_3 in $OCOCH_3$)

[a] w = weak, m = medium, s = strong, vw = very weak, vs = very strong.
[b] Total number of assigned carbon atoms referred to the overall scheme (C_{259}).

two signals of medium intensity at 171.8 and 20.8 ppm can be assigned to acetyl groups probably bonded to residual hemicelluloses[43]. When deuterated dioxane is used as solvent, the band at 171.8 ppm possesses a shoulder which can be

attributed to the ester carbonyl carbon atom assumed between the C_9 units nos. 13 and 20 in the proposed structure. All the other signals of the lignin ^{13}C-NMR spectrum differ at most by 1 ppm from those of the "calculated spectrum".

7. Outlook

Lignin is a high-molecular natural product: the ultimate step in its formation is a free-radical coupling of monomeric units which is not subjeet to enzymatic control. Hence lignin differs from other natural products, such as proteins, nucleic acids, and polysaccharides, in which the bonding of the monomeric units and their sequence is determined, by having a random distribution of at least ten different kinds of bonds. Thus any structural scheme proposed for lignin can only represent the average distribution of these bonds, which also reflects to some extent on its elemental analysis. Nevertheless, the proposed structural scheme (Fig. 4) based solely on the results of lignin degradation, must be open to biogenetic interpretation. The fulfilment of this requirement constitutes further proof of *Freudenberg*'s proposal that lignin is formed by oxidative coupling of *p*-hydroxycinnamyl alcohols.

Future structural studies on lignin from other sources, taxonomic studies, and investigation of chemical changes in lignin during industrial wood processing will find an exceptionally powerful tool in ^{13}C-NMR spectroscopy. With the aid of the spectra recorded for more than fifty lignin model substances, all the important signals in the ^{13}C-NMR spectra of coniferous and deciduous lignin can now be assigned. Moreover, comparison of the intensities of corresponding signals in the ^{13}C-NMR spectra of different lignins permits interesting structural comparisons. The technique of comparing calculated and recorded spectra adopted here can also be applied to other lignins.

We are well aware that any lignin formula is open to improvement. In our case this applies particularly with regard to the number of free phenolic groups resulting on drawing the proposed structure and the number of benzyl alcohol and benzyl ether groups for which no reliable analytical determinations have yet been completed. In our opinion, the main value of the proposed structural scheme lies in the clarity it brings to the century-old problem of the structure of lignin, which attracts the interest of chemists, botanists, forestry scientists, and wood technologists. For instance, our scheme recently provided a ready explanation of the discoloration of celluloses containing lignin[52].

The immense problem of finding industrial applications for lignin, which is highly topical in view of environmental pollution, remains a great challenge to the cellulose and lignin chemist. The inherent difficulty of economic degradation of lignin to give low-molecular weight products of industrial value is apparent from the formula given above. It might, however, stimulate the search for new techniques. Only very limited quantities of vanillin and several sulfur compounds, such as methanethiol, dimethyl sulfide and its oxidation products, have so far been produced from the waste liquors from pulp mills. Hydrogenolytic "lignin liquefaction"[53] at high temperatures and hydrogen pressures has not yet found industrial application, presumably owing to competition from natural gas and oil. However, the day is approaching when we shall have to take recourse to lignin as an organic raw material constantly being replenished by nature.

In high-molecular form lignin is currently used as an additive for concrete, drilling muds, storage battery plates, synthetic resins and rubber, and also as dispersing agents, as binders for road surfacing materials and for biquetting or pelletizing of ores, coal, and animal feeds, as adhesive for floor coverings, and for numerous other purposes. However, the amount of lignin utilized is but a fraction of the total amount produced.

We recently found[54] that, owing to their content of phenol groups with free *ortho* positions, water-soluble ligninsulfonic acids occurring in industrial waste sulfite liquors can be effectively crosslinked under mild conditions by oxidative coupling and hence rendered insoluble. The products can be used as ion-exchangers. In addition, wood chips can be pressed with sulfite waste liquor in the presence of an oxidizing agent and a catalyst to give a particle board having excellent strength and satisfactory properties under moist conditions. Since the current consumption of wood for particle boards in the Federal Republic of Germany is of the same order as that for cellulose production this could represent an adequate application for the lignin obtained in pulp mills.

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[1] Pulp and Paper 42, "18th Annual World Review" (1968).

[2] *K. Freudenberg* and *A. C. Neish*: Constitution and Biosynthesis of Lignin. Springer, Berlin 1968.

[3] *K. V. Sarkanen* and *C. H. Ludwig*: Lignins. Wiley-Interscience, New York 1971.

[4] *F. E. Brauns*: The Chemistry of Lignin. Academic Press, New York 1952; *F. E. Brauns* and *D. A. Brauns*: The Chemistry of Lignin, Supplement Volume. Academic Press, New York 1960.

[5] *F. Schütz, P. Sarten*, and *H. Meyer*, Angew. Chem. 60, 115 (1948); cf. *R. S. Hilpert* and *E. Littmann*, Ber. Deut. Chem. Ges. 67, 1551 (1934).

[6] Cf., *e.g.*, *K. Freudenberg, C. Harder*, and *L. Markert*, Ber. Deut. Chem. Ges. 61, 1760 (1928); *K. Freudenberg, W. Lautsch*, and *G. Piazolo*, Cellul.-Chem. 21, 95 (1943).

[7] *P. W. Lange*, Sv. Papperstidn. 47, 262 (1944); 53, 749 (1950).

[8] *K. Kratzl* and *H. Tschamler*, Monatsh. Chem. 83, 786 (1952).

[9] *P. Klason*, Ark. Kemi, Mineral Geol. 2, 36 (1907); 4, No. 6 (1911).

[10] *K. Freudenberg, W. Belz*, and *C. Niemann*, Ber. Deut. Chem. Ges. 62, 1554 (1929).

[11] *K. Freudenberg* and *W. Dürr*, Ber. Deut. Chem. Ges. 63, 2713 (1930).

[12] *K. Freudenberg, F. Sohns, W. Dürr*, and *C. Niemann*, Cellul.-Chem. 12, 263 (1931).

[13] *E. E. Harris, J. D'Ianni*, and *H. Adkins*, J. Amer. Chem. Soc. 60, 1467 (1938).

[14] *A. B. Cramer, J. M. Hunter*, and *H. Hibbert*, J. Amer. Chem. Soc. 61, 509 (1939).

[15] *H. Erdtman*, Liebigs Ann. Chem. 503, 283 (1933); Biochem. Z. 258, 172 (1933); *H. Cousin* and *H. Herissey*, C. R. Acad. Sci. 146, 1413 (1908); 147, 247 (1909).

[16] *F. Tiemann* and *B. Mendelsohn*, Ber. Deut. Chem. Ges. 8, 1136 (1875).

[17] *K. Freudenberg*, Holzforschung 18, 3 (1964); *K. Freudenberg* and *J. M. Harkin*, ibid. 18, 166 (1964).

[18] *K. Freudenberg* and *G. S. Sidhu*, Holzforschung 15, 33 (1961).

[19] *E. Adler* and *B. O. Lindgren*, Sv. Papperstidn. 55, 563 (1952); *E. Adler, J. M. Pepper*, and *E. Eriksoo*, Ind. Eng. Chem. 49, 1391 (1957).

[20] *K. Lundquist*, Acta Chem. Scand. 18, 1316 (1964).

[21] *H. Nimz*, Holzforschung 23, 84 (1969).

[22] *K. Kratzl, J. Zauner*, and *P. Claus*, Holzforschung 18, 47 (1964); *K. Kratzl*, Pap. Timber 11, 643 (1961).

[23] *K. Freudenberg, J. M. Harkin*, and *H.-K. Werner*, Chem. Ber. 97, 909 (1964).

[24] *E. Adler, H.-D. Becker, T. Ishihara*, and *A. Stamvik*, Holzforschung 20, 3 (1966).

[25] *H. Nimz*, Chem. Ber. *98*, 3153 (1965).

[26] *H. Nimz*, Chem. Ber. *98*, 533 (1965).

[27] *H. Nimz*, Habilitationsschrift, Universität Heidelberg 1967.

[28] *H. Nimz* and *H. Gaber*, Chem. Ber. *98*, 538 (1965).

[29] *H. Nimz*, Chem. Ber. *98*, 3160 (1965); *99*, 469, 2638 (1966); *100*, 181, 2633 (1967); Holzforschung *20*, 105 (1966).

[30] *K. Freudenberg* and *H. Nimz*, Chem. Commun. *1966*, 132.

[31] *K. Lundquist* and *G. E. Miksche*, Tetrahedron Lett. *1965*, 2131.

[32] *H. Nimz*, Chem. Ber. *102*, 799 (1969).

[33] *H. Nimz*, Chem. Ber. *102*, 1803 (1969).

[34] Cf. *J. Gierer* and *L. A. Smedman*, Acta Chem. Scand. *19*, 1103 (1965); *20*, 1769 (1966).

[35] *J. Bougault*, *E. Cathelain*, and *P. Charbrier*, C. R. Acad. Sci. *208*, 657 (1939); *R. Mozingo*, *D. E. Wolf*, *S. A. Harris*, and *K. Folkers*, J. Amer. Chem. Soc. *65*, 1013 (1943).

[36] *H. Nimz*, *K. Das*, and *N. Minemura*, Chem. Ber. *104*, 1871 (1971).

[37] *H. Nimz* and *K. Das*, Chem. Ber. *104*, 2359 (1971).

[38] *K. Lundquist*, *G. E. Miksche*, *L. Ericsson*, and *L. Berndtson*, Tetrahedron Lett. *1967*, 4587.

[39] *A. Björkman* and *B. Person*, Sv. Papperstidn. *60*, 158 (1957).

[40] *G. Aulin-Erdtman*, Sv. Papperstidn. *56*, 91 (1953); *G. Aulin-Erdtman* and *L. Heybom*, *ibid. 60*, 671 (1957); *G. Aulin-Erdtman* and *R. Sanden*, Acta Chem. Scand. *22*, 1187 (1968).

[41] *E. Adler*, Pap. Timber *11*, 634 (1961).

[42] *L. Šutý* and *E. Golis*, Cellul. Chem. Technol. *6*, 485 (1972).

[43] *T. E. Timell*, Sv. Papperstidn. *60*, 762 (1957); *D. F. Packman*, Holzforschung *14*, 178 (1960); *W. Sandermann*, Deut. Ges. Holzforsch., Nachr. *3*, 8 (1968).

[44] *C. H. Ludwig* in [3], p. 299.

[45] *C. H. Ludwig*, *B. J. Nist*, and *J. L. McCarthy*, J. Amer. Chem. Soc. *86*, 1196 (1964).

[46] *D. E. Bland* and *S. Sternhell*, Nature *196*, 985 (1962).

[47] *E. Stahl*, *F. Karig*, *U. Brögmann*, *H. Nimz*, and *H. Becker*, Holzforschung *27*, 89 (1973). No hemicelluloses could be detected in spruce MWL by this method.

[48] *A. Björkman*, Sv. Papperstidn. *59*, 477 (1956).

[49] *M. A. Latif*, Dissertation, University of Washington, Seattle 1968; cited according to [3].

[50] *E. Breitmaier*, *G. Jung*, and *W. Voelter*, Angew. Chem. *83*, 659 (1971); Angew. Chem. internat. Edit. *10*, 673 (1971); *J. B. Stothers*, Carbon-13 NMR Spectroscopy, Academic Press, New York 1972.

[51] *H.-D. Lüdemann* and *H. Nimz*, Biochem. Biophys. Res. Commun. *52*, 1162 (1973); Makromol. Chem., in press.

[52] *H. Nimz*, Tappi *56*, No. 5, 124 (1973).

[53] *J. Giesen*, US-Pat. 2991314 (1961), and earlier patents; *M. Oshima*, *Y. Meeda*, and *K. Kashima*, Canad. Pat. 700209 (1964), and earlier patents; *W. Schweers*, Holzforschung *23*, 5 (1969); *J. M. Pepper* and *Y. W. Lee*, Can. J. Chem. *47*, 723 (1969); *48*, 477 (1970).

[54] *H. Nimz*, *A. Razvi*, *I. Mogharab*, and *W. Clad*, DBP 2221353 (1972); Helmitin-Werke Pirmasens.

[55] *W. Schweers* and *O. Faix*, Holzforschung *27*, 208 (1973).

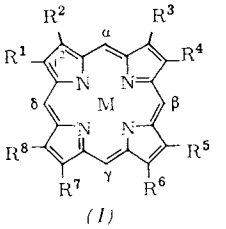
The Reactivity of the Porphyrin Ligand[**]

By Jürgen-Hinrich Fuhrhop[*]

The physical properties and the chemical reactivity of the porphyrin macrocycle, whose formation can be rationalized by a simple statistical argument, are related in many respects to those of aromatic hydrocarbons. The reactivity of the porphyrin ligand in its metal complexes varies within wide limits because of the difference in the inductive effects of different central metal ions on the conjugated π-electron system. One-electron reactions, phlorin formation by addition of hydrogen or oxygen to the methine bridges, and the formation of π complexes predominate. The biochemical reactivity of the porphyrin ligand largely corresponds to its *in-vitro* chemistry.

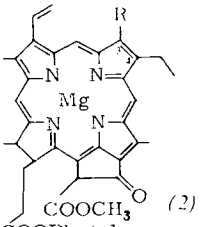
1. Introduction

Metal-porphyrin complexes[***] *(1)* occur extremely widely in biological redox systems, *e. g.* redox chains of photosynthesis and of respiration. The rigid, planar porphyrin ligand fulfills two main functions here. On the one hand it fixes the redox-active iron ions in a reactive center and at the same time modifies their oxidation potential by the formation of covalent nitrogen-metal bonds in the plane of the porphyrin. A metallic reaction center of this type is involved in the electron transfer in redox chains in the cytochromes[1], is capable of reversibly adding on oxygen in hemoglobin[2], and also plays a part in the activation of molecular oxygen in oxidizing enzymes[3]. These "inorganic" reactions of metal-porphyrin complexes will not be discussed further here.



(1)

Porphin: R^1-R^8 = H, M = 2 H



(2)

Chlorophyll a: R = CH_3
Bacteriochlorophyll: R = CHO, hydrogenated at 3, 4

On the other hand, the macrocyclic porphyrin ligand can also assume the role of the redox active center. The most important example of this is that of the chlorophylls *(2)*,

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[**] Parts of this progress report are taken from the author's Habilitation Dissertation, Technische Universität Braunschweig 1972.

[***] Note on nomenclature: As far as we know, there are as yet no definitive IUPAC rules for this class of compounds. The macrocycle consisting of four pyrrole rings and four methine bridges is known as porphyrin. Systems with partly hydrogenated pyrrole rings may be referred to as chlorins: those with one, two, three, and four hydrogenated methine bridges are called phlorins, porphodimethenes, porphomethenes, and porphyrinogens, respectively. The porphyrin having only hydrogen atoms as subsituents is termed porphin (see also *K. Bonnett*, Ann. N.Y. Acad. Sci. *206*, 745 (1973)).

with whose aid the sunlight absorbed by photosynthetically active organisms is converted into chemical redox energy (Fig. 1).

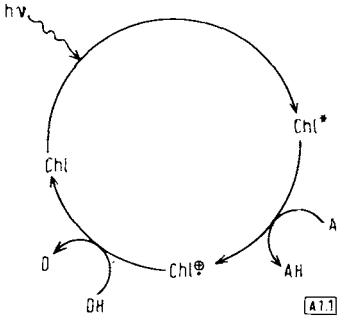


Fig. 1. Scheme of the primary steps of the photosynthesis [4]: an excited chlorophyll molecule (Chl*) transfers its high-energy electron to an acceptor molecule (A) and the resulting chlorophyll radical-cation oxidizes a donor molecule (D). The result of this cycle is the conversion of the absorbed light energy into chemical energy.

This active role of a porphyrin ligand in redox reactions first became evident in 1953 when *Commoner*[5], by EPR spectroscopy, detected the occurrence of organic free radicals on irradiation of photosynthetically active organisms, these radicals rapidly disappearing again in the dark. The formation of chlorophyll radical-cations in the photosynthetically active center has now been conclusively demonstrated, and the scheme of Figure 1 has been confirmed in broad outline many times[6], with the result that interest has been centered on the reversible formation of free radicals of the metal-porphyrin complexes. Other biologically important activities in which porphyrin ligands are directly involved concern the irreversible addition of oxygen to ironporphyrin complexes, which ultimately leads to cleavage of the macrocycle and formation of bile pigments[7-10], and the weak interaction of the porphyrin π-electron system with other biological redox catalysts, which may play a part in the electron transfer from chlorophyll to the oxidizing agent A (Fig. 1)[11].

The specific reactivity of the porphyrin ligand, in nearly every case, was first detected in biological systems and only later demonstrated *in vitro*. The surprising fact that the fundamental reactions of the porphyrin ligand were systematically studied and largely elucidated only in the last decade, and were able to escape the notice *e.g.* of *Hans Fischer* for such a long time, can be explained by the superiority of modern spectroscopic and electrochemical methods, which only now allow a reliable distinction between nonspecific destruction and a chemically definite, uniform reaction of the porphyrin ligand. We can be sure, for example, that *Hans Fischer* observed the formation of many of the brown and brown-green radicals and oxygenation products of metal-porphyrin complexes, but discarded them after a glance through the hand spectroscope.

However, interest in the reactivity of porphyrin ligands is not confined to biological aspects. A simple model of the porphyrin ring that was proposed in 1949[12] and has been continuously refined since then[13,14] stylizes the basic skeleton of this tetrapyrrole pigment to a cyclic planar hydrocarbon with 18 π electrons, which, according to the Hückel rule, should be particularly stable and should exhibit aromatic character. The fact that many different metal ions can be introduced into the center of this conjugated π-electron system suggests the possibility of varying the chemical reactivity of an aromatic system within wide limits by metal substitution and of systematically investigating the underlying interactions for the first time. This brings the chemistry of the porphyrin ligand within the ambit of general organic and inorganic chemistry beyond the aspects of natural product chemistry.

2. The Formation of the Porphyrin Macrocycle from Monomeric Pyrrole Units

The structure (Fig. 2) suggested for hemin by *Küster* in 1913[15] was not accepted at first either by *Willstätter* or by *H. Fischer*. Their reluctance is easy to understand: no natural product with a comparable ring size was known, and the directed synthesis of a sixteen-membered macrocycle seemed beyond the reach of the methods known at that time. However, a

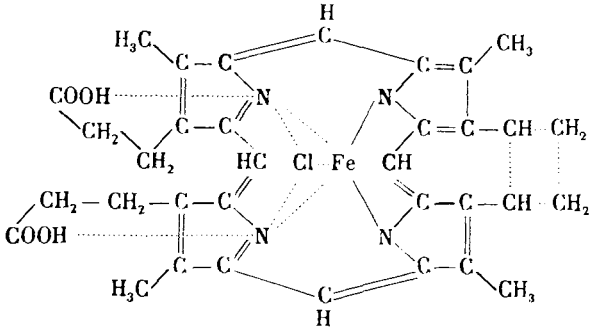
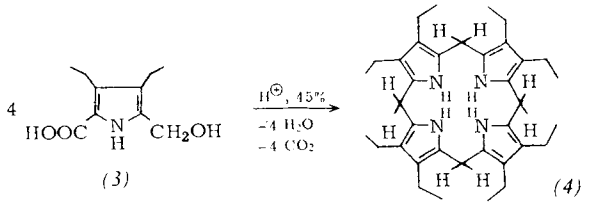


Fig. 2. *Küster*'s original structure for hemin from 1913 [15]. The position of a vinyl group is wrong, but all other structural data correspond to the present-day views. A particularly interesting feature is the suggested interactions of axial ligands and propionic acid side chains with the porphyrin ring, the importance of which is still a matter for speculation.

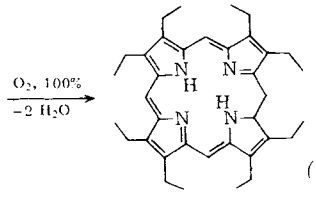
"directed" synthesis in the sense of a special ring-closure reaction is not really necessary. The simple condensation of partly or completely α-unsubstituted pyrroles such as *(6)*, *(8)*, and *(10)*, leads to high yields of porphyrin analogs under a wide range of conditions, regardless of whether the bridges in the primary product are saturated (porphyrinogens, phlorins) or unsaturated (porphyrins).

The porphyrinogens such as *e.g. (9)*, which are usually formed first, are quantitatively oxidized to porphyrins by oxidizing agents, *e.g.* oxygen. It is only in this oxidized state that the macrocycle is stable to acids. Methylene bridges, on the other hand, are readily broken by protons, and in the case of porphyrinogens this leads to decompositions and isomerizations[22].

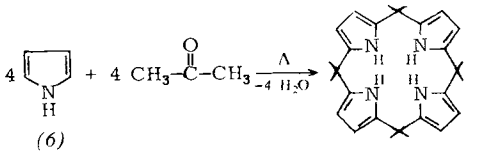
This surprisingly simple solution to the problem of the synthesis of the porphyrin ring (the enzyme-controlled biosynthesis follows a course similar to that of the reaction *(8)*→*(9)*[23,24]) now also reveals the simple principle that causes the ring closure to occur in high yields after a linear tetramerization of the pyrrole units has taken place: the formation of a strain-free macrocycle by intramolecular condensation is possible only from the tetramer on, and this reaction is several orders of magnitude more probable than the addition of a fifth pyrrole ring. The maximum distance between the two reaction centers in the intermediate *(12)* is 18 Å, and the mean distance $\bar{r}$ is 8 Å (from $\bar{r}^2 = 2l^2 \times Z$[25], where $l = 1.4$ Å



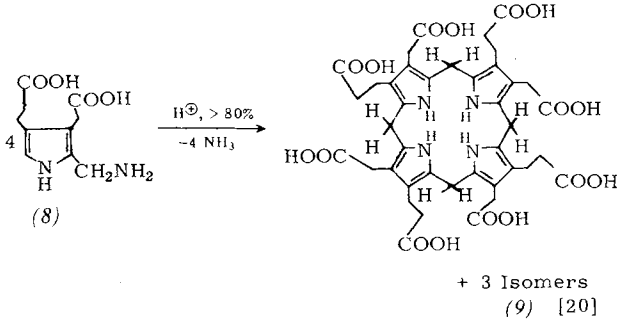
(3) (4)



(5) [16, 17]

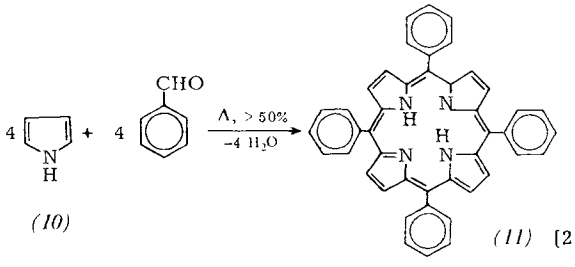


(6) (7) [18,19]



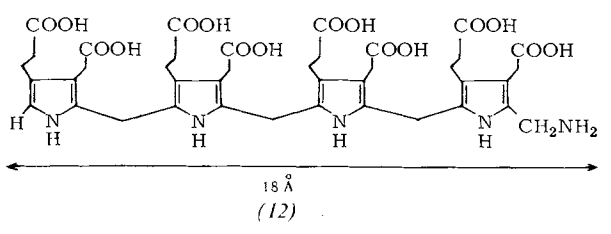
+ 3 Isomers

(8) (9) [20]



(10) (11) [21]

and $Z = 16$ are the mean bond length and the number of atoms in the chain); these values correspond to concentrations of 0.5 and 4 mole/l respectively[20]. This concentration range is many orders of magnitude greater than that of the tetrapyrromethane intermediate in the *in-vitro* and *in-vivo* syntheses, and the simple statistical argument is therefore sufficient to explain the formation of the macrocycle. No special matrix is necessary.



18 Å

(12)

The main condition for such a cyclization is that the activation energy of the intramolecular reaction should be comparable with that of the competing bimolecular reaction. This condition is satisfied in the formation of porphyrinogens: the unsubstituted α-pyrrole position of a pyrromethane is practically as reactive as that of an analogous unsubstituted pyrrole[26]. Under these circumstances the fact that other important products of polycondensations in biological systems, *e.g.* amino acids, nucleic acids, and sugar phosphates, have only one reactive end explains why the spontaneous, almost quantitative formation of macrocycles is confined to the porphyrinogen system. Finally, it should also be pointed out that β-unsubstituted pyrrole carbon atoms are also very reactive in the condensation in acidic solution; this leads to nonspecific condensations. The unsubstituted porphin [cf. *(1)*] cannot therefore be prepared by *Siedel*'s method [*(3)*→*(5)*], which is so successful for octaalkylporphins; it is best synthesized by free-radical oligomerization and ring closure[27].

3. Metal-Porphyrin Complexes and the [16]Annulene-diyl Dianion

The porphin macrocycle contains eleven conjugated double bonds, but only nine of these are required to form a fully conjugated cyclic polyene (Fig. 3a).

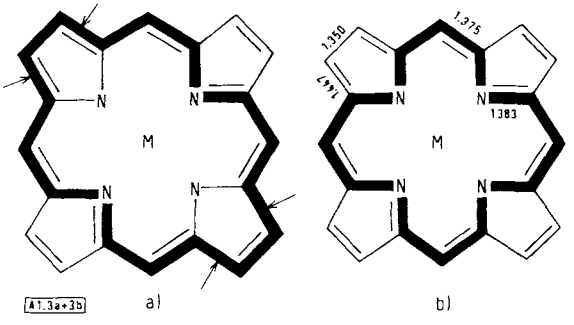


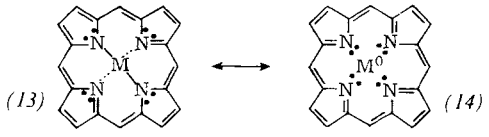
Fig. 3. a) The "outer" conjugation path [51] of the metal-porphin complexes, which is formally the shortest conjugation path [cf. with *(13)*]. It passes through a total of four α,β-pyrrole bonds (arrows), which are distinctly longer than in a corresponding aromatic system. b) The "inner" conjugation path [51] of metal-porphin complexes, in which only bond lengths corresponding to those of comparable aromatic compounds occur [cf. with *(14)*]. The bond lengths indicated (in Å) were measured for tetraphenylporphinatonickel [28].

If the two nitrogen atoms involved are regarded, to a first approximation, as equivalent to methine groups, in accordance with the Grimm hydride shift theory, [18]annulene could be taken as a model to describe porphin. However, the well-resolved X-ray structural analysis of a porphinatonickel derivative[28] showed that all the bond lengths of the inner ring (thick lines in Fig. 3b) are equal, and are close to those of aromatic compounds (*e.g.* $C—C_{benzene} = 1.395$ Å, $C—N_{pyridine} = 1.352$ Å)[29].

The length of the α,β-pyrrole C—C bond, on the other hand, corresponds to that of a C—C single bond in a conjugated polyene (*e.g.* $CH_2=CH—C\equiv N = 1.44$ Å)[29].

From the purely formal standpoint, this last result can be better represented by an electron distribution as shown in *(14)* for metal-porphin complexes than by the usual notation *(13)*, which still reflects the D_{2h} symmetry of the free porphin. If the outer conjugation system is taken into account, as in the [18]annulene model of Figure 3a, different bond lengths would have to be introduced, following the

results of the X-ray structural analysis. A more elegant model is obtained if one considers only the inner conjugation system, which is in contact with the central metal ion, and which is best characterized as the [16]annulenediyl dianion (Fig. 3b). The nitrogen atoms are again replaced by methine groups, and two electrons of the metal ion are also included.



The electronic spectrum of this polyene can be best explained by a model in which all 18 electrons are given a molecular orbital angular momentum that can be figuratively attributed to rotation about the porphin ring[12]. Since orbiting to the left and to the right (positive and negative angular momentum quantum numbers) are equal in energy in the absence of magnetic and electric fields, this postulate leads to singly degenerate energy levels when the angular momentum is different from zero, and hence to the qualitative energy diagram shown in Figure 4 for our simple porphin model.

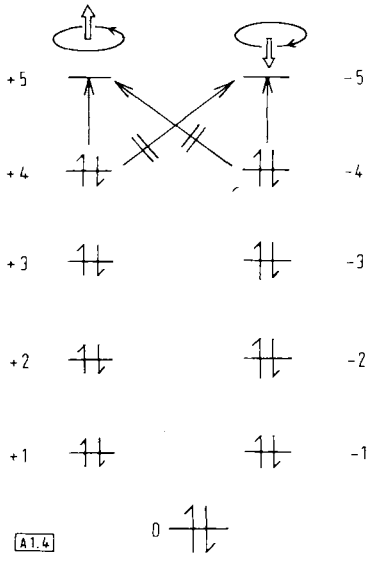


Fig. 4. Qualitative energy level diagram of the porphin ligand with the corresponding angular momentum quantum numbers as given by the simplest free-electron model [12, 30]. The arrows correspond to "allowed" (→) and "forbidden" (↛) electron transitions of lowest energy between the degenerate frontier orbitals. This simple model is sufficient for the interpretation of the most important physical properties of the porphin ring.

The ground state has a closed shell with no resultant angular momentum. The excited singlet states, on the other hand, which are indicated by the arrows, give a resultant angular momentum of ± 1 if the electronic transition takes place between energy levels having the corresponding quantum numbers with the same sign, or ± 9 if the sign changes. The former transition is "allowed" according to *Hund*'s rules, and was assigned to the intense short-wave Soret band of the porphyrins, whereas the latter is "forbidden" and so corresponds to the visible bands that are weaker by a factor of ten (see *e.g.* spectrum a in Fig. 5).

If the electronic excitation takes place while the molecule is in an external magnetic field H_0, the degeneracy of the energy levels is partly eliminated, since the magnetic fields

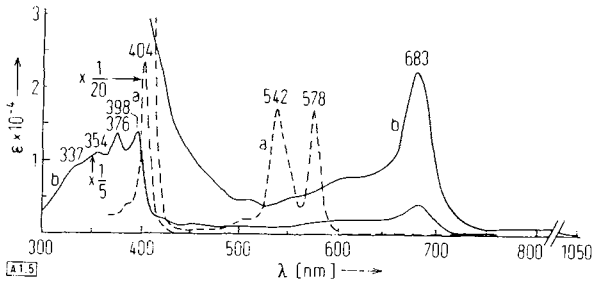


Fig. 5. Electronic spectra of octaethylporphinatomagnesium (spectrum a) and its one-electron oxidation product, the π-radical-cation (spectrum b) [32].

resulting from the "orbiting of the electrons to the left and to the right" interact differently with the external magnetic field (Zeeman effect), the splitting ΔE being proportional to the orbital angular momentum L. Measurement of the Zeeman effect on a porphinato-zinc derivative in DMSO with circularly polarized light gave an angular momentum of $L = 9.5 \pm 0.6$ units for the visible α band and about 1.3 units for the Soret band[30]. This has provided surprising confirmation of the extremely simple free-electron model; the single degeneracy of the highest occupied and of the lowest unoccupied energy levels seems to have been verified experimentally. The interpretation of the Zeeman effect for metal-porphyrin complexes has now been further refined[31], but this has had no effect on the essential consequences.

It has recently also become possible to support the analogy between the porphyrin ligand and the [16]annulenediyl dianion by comparison of the electronic spectra of the two compounds (Fig. 6).

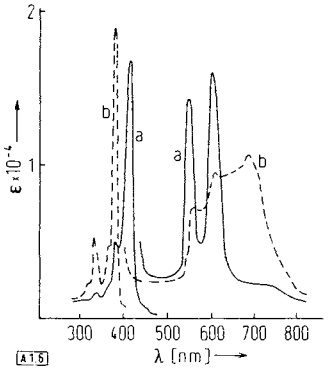


Fig. 6. Electronic spectra of the [16]annulenediyl dianion (spectrum a) and its one-electron oxidation product, the π-radical-anion (spectrum b) (after [33]). Compare Figure 5.

The spectra of octaethylporphinatomagnesium[32] and of the [16]annulenediyl dianion[33] are practically identical, as are those of the π-electron systems with one electron less. The diamagnetic ring currents as found from NMR measurements are also very similar for the two macrocycles[33, 34]. Beyond these simple arguments by analogy based on physical measurements, however, a comparison of the two macrocycles is probably not very fruitful, mainly because of their very different stabilities.

The physical measurements show clearly the benzene-like character of the porphyrin ligands, in the sense that the bond lengths of the inner conjugation system do not alternate and the outside orbitals are singly degenerate. Extended Hückel model calculations led to the same result[13, 14].

4. Central Metal Ions

The chemistry of the central metal ions in metal-porphyrin complexes will be discussed here only insofar as this is necessary to clarify the most important interactions between the porphyrin ligand and the metal ion. Nearly all metals, with the exception of the lanthanoids and actinoids, are now known to be able to form complexes with the porphyrin ligand[35, 36]. The porphyrin ligand is planar in all the metal complexes investigated so far; the decisive bonding factor is the donation of σ electrons from the four nitrogen atoms to the central metal ion, which always leads to stabilization of formally relatively high oxidation states: the σ electrons of the porphyrin ligand neutralize the positive charge on the metal ion and occupy the orbitals of the metal that can enter into σ and π bonds in the plane of the porphyrin with the four nitrogen atoms (mainly s and p orbitals in the metals of the main groups and the $d_{x^2-y^2}$ and d_{xy} orbitals in the transition metals).

The effect of a strong covalent σ bond in a planar ligand field on the metal ion can be briefly demonstrated by an example. Porphinatosilver(II) complexes (a d^9 system with an unpaired electron in the $d_{x^2-y^2}$ orbital) can be oxidized by iron(III) salts to stable, diamagnetic porphinatosilver(III) complexes ($E^{ox}_{1/2} = 440$ mV, SCE)[37]. The only other route by which this oxidation stage has so far been reached is by persulfate oxidation of a guanidine derivative, which is probably also planar[38], whereas *e.g.* the Ag^{II}/Ag^{I} pair in perchloric acid has an equivalence potential of $+1.76$ V[39], a potential at which all organic compounds would be destroyed. The extreme stabilization of the unusual Ag^{III} oxidation stage (a d^8 system) is a good indication of the extreme electron donor capacity of the planar porphyrin ligand. The direct interactions between the metal ion and the porphyrin ligand by π bonds normal to the plane of the porphyrin are negligible by comparison.

5. π-Radical-Cations and π-Radical-Anions of Metal-Porphyrin Complexes

The simplest reaction of an aromatic compound such as *(16)* is its reversible one-electron oxidation or reduction to form the radical-cation *(15)* or the radical-anion *(17)*.

$$C_{10}H_8^{\oplus\bullet} \underset{+e^{\ominus}}{\overset{-e^{\ominus}}{\rightleftharpoons}} C_{10}H_8 \underset{+e^{\ominus}}{\overset{-e^{\ominus}}{\rightleftharpoons}} C_{10}H_8^{\ominus\bullet}$$

(15) *(16)* *(17)*

The electron is removed here from the highest occupied π orbital (≡highest occupied molecular orbital, "HOMO") or introduced into the lowest unoccupied molecular orbital ("LUMO"). These two orbitals are also known as the frontier orbitals. In alternating aromatic molecules the potentials of the one-electron oxidation (reduction) are proportional to the energies of the highest bonding (lowest antibonding) orbital: the higher the energies of the frontier orbitals, the more difficult do oxidation and reduction become. If the reduction potentials of a series of aromatic hydrocarbons are plotted against their oxidation potentials, the result is a straight line with a slope of about -1; this means that an increase in the oxidation potential corresponds to an approximately equal increase in the reduction potential[40], (Fig. 7). This behavior is as expected[40] since the energy eigenvalues of the bonding and antibonding frontier orbitals in alternant hydrocarbons differ only in sign.

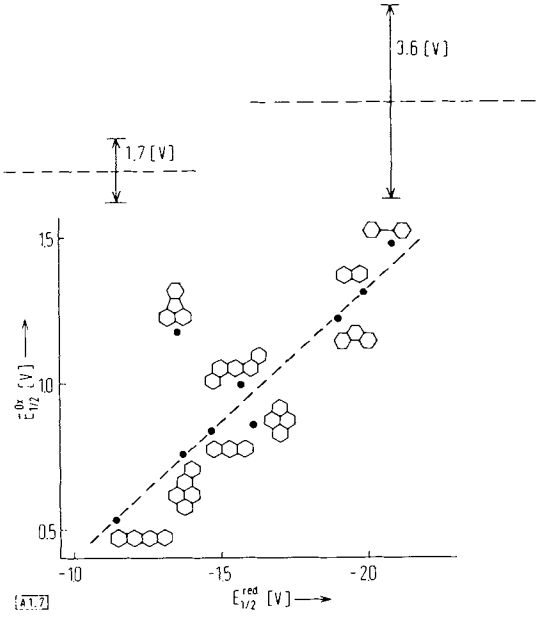
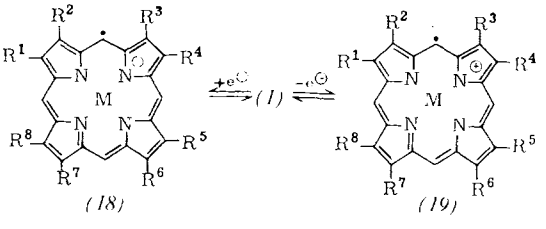


Fig. 7. Half-wave potentials of the one-electron oxidation and reduction of several alternant aromatic hydrocarbons [40]. The linear relation between the two potentials follows from the observation that the redox potentials are linear functions of the eigenvalue coefficients of the outermost orbitals, which are symmetrical with respect to the non-bonding energy level ( ) [40]. The difference $E^{ox}_{1/2} - E^{red}_{1/2}$ is about 1.7 V for tetracene, the most reactive member of the series, and increases to about 3.6 V for biphenyl. (Only the skeletons of the molecules are shown.)

Metal-porphyrin complexes *(1)* also form π-radical-cations *(19)*[32, 41, 44], or π-radical-anions *(18)*[42, 43] on chemical, photochemical or electrochemical oxidation or reduction. Titration of octaethylporphinatomagnesium *(1)*, M = Mg, R^1 $R^8 = C_2H_5$, with $FeCl_3$ in methanolic solution leads to the changes in absorption shown in Figure 8. It has been shown by paramagnetic resonance measurements on the same solutions that the product of the oxidation is quantitatively present



as the free radical[32]. Similar titrations in which the potential of the solution was also followed showed that the equivalence potential in the oxidation of porphyrins is strongly dependent on the central metal ion: the more electronegative this ion is, the more electrons it withdraws from the porphyrin ligand, and the more difficult it becomes to oxidize the latter[37, 41]. A linear relation has even been demonstrated between the one-electron oxidation potential of the porphyrin ligand and the electronegativity of the metal ion in the case of stable bivalent ions (Fig. 9)[41, 45].

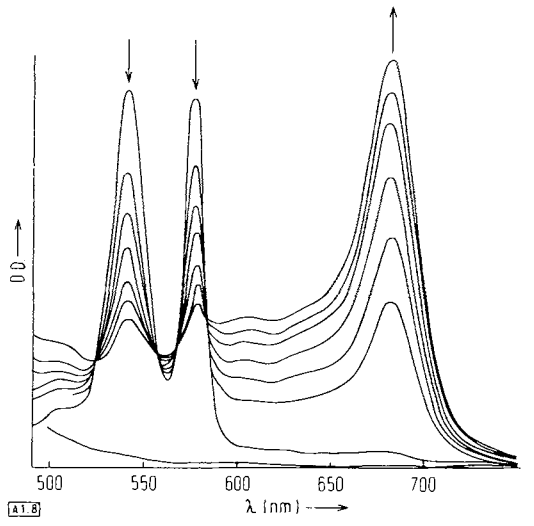


Fig. 8. Chemical oxidation of octaethylporphinatomagnesium in methanol with $FeCl_3$ followed spectrophotometrically.

Such simple relations are no longer observed with ions having higher valencies (*e.g.* Al^{III}, Fe^{III}, *etc.*). In most cases the redox potentials can only be measured polarographically or voltam-

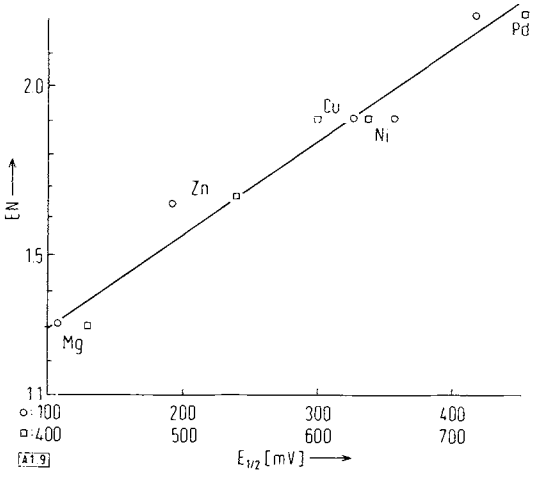


Fig. 9. Midpoint potentials of five metal complexes of octaethylporphin (□) and octaethylchlorin (○) as a function of the electronegativity (EN) of the bivalent central metal ions [45]. (Chlorin is 1,2-dihydroporphin.)

metrically, but a linear relation is still found between the one-electron oxidation and reduction potentials of the porphyrin ligand for nearly all the metal-porphyrin complexes investigated (Fig. 10)[37,41].

A comparison of the straight lines in Figures 7 and 10 immediately shows the characteristic difference in the underlying phenomena. In the conjugation system of Fig. 7 a low oxidation potential is coupled with a low reduction potential, whereas the introduction of metal ions into the porphyrin ligands leads to the opposite situation: a metal ion that has a low tendency to withdraw electrons from the porphyrin ligand (*e.g.* Mg^{II}) activates the ligand for oxidation and deactivates it for reduction[32,37,41]. The corresponding behavior with strongly electron-attracting metals (*e.g.* Sn^{IV}) leads to greater ease of reduction of the porphyrin ligand and to extraordinary stability toward oxidizing agents[65]. The regularity of the redox reactions of metal-porphyrin complexes demonstrated in Figure 10 is a good indication of the dominant role played by the strong inductive action of the central metal ion on the π-electron system of the porphyrin ligand, and shows in turn that d(*xz*,*yz*) interactions hardly occur, since there would otherwise be no explanation for the similarity of the effects of main-group metal and transition metal ions. The

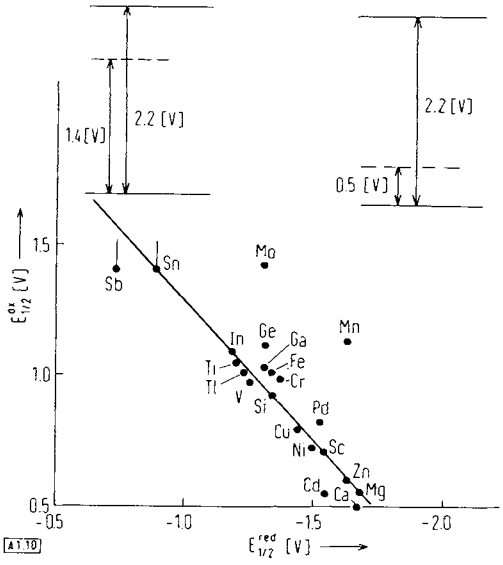


Fig. 10. Half-wave potentials of the one-electron oxidation and reduction of the octaethylporphin ligand in its metal complexes. The greater the difficulty of oxidation of the porphyrin ligand in a complex, the easier is its reduction, and *vice versa*. This behavior points to an inductive effect of the central metal ions, which causes a displacement of the two frontier orbitals of the porphyrin in the same direction in relation to the non-bonding energy-level (---) (cf. Fig. 7).

values of the oxidation and reduction potentials fluctuate by about 1 volt, but the difference between the two potentials for a given metal-porphyrin complex is practically constant ($E^{ox}_{1/2} - E^{red}_{1/2} = 2.25 \pm 0.15$ V). It should also be mentioned here that this energy difference is reproduced extremely well (2.18 eV) by calculations based on the extended Hückel model, whereas the inductive effects of the central metal ions play practically no part in this model[46].

However, Figure 10 also contains two complexes that show very strong deviations, *i.e.* the octaethylporphinato complexes of manganese and of molybdenum. In both cases the difference between the potentials increases to about 2.8 V, and unusual splitting of the Soret band is observed in the electronic spectrum in both cases[47,48]; this has been attributed in the case of Mn^{III} to interactions of the π electrons of the metal and of the porphyrin ligand. It is tempting to conclude that these interactions normal to the plane of the porphyrin cause extra stabilization of one oxidation state in this case, but further experimental support is needed for this conclusion.

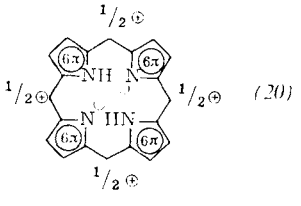
Figure 9 also contains a point of general interest: the conjugation system of chlorophyll *(2)* with a reduced peripheral double bond in a pyrrole ring (chlorins) has an oxidation potential in its metal complexes that is about 300 mV lower than that of the analogous metal-porphyrin complexes[45]. A decrease in potential by about 300 mV has also been observed between chlorophyll and bacteriochlorophyll, which has two reduced pyrrole rings[32]. This fact is probably related to the *in-vivo* observations that magnesium-porphyrin complexes have toxic effects in plants under the action of light and that much lower oxidation potentials are reached in bac-

terial photosynthesis than in plant photosynthesis. The greater ease of oxidation of metal-porphyrin complexes with partly hydrogenated pyrrole rings also finds qualitative confirmation in theoretical model calculations: a somewhat higher energy eigenvalue is found for the highest bonding orbital in the chlorins and bacteriochlorins[49].

Many of the radical-anions and radical-cations have been obtained in the crystalline state and their electronic and EPR spectra analyzed in detail[44, 50, 99]; recently, even the X-ray structure of a π radical has been reported[100]. Diamagnetic π-dications[44] and π-dianions[42] have also been obtained. By far the most interesting secondary products of the redox reactions of porphyrins, however, are the phlorins, which were discovered independently by *Mauzerall*[22, 52] and *Woodward*[53, 54] about 15 years ago.

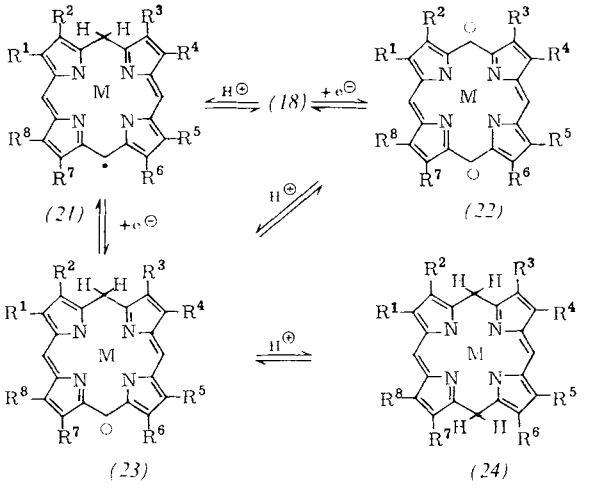
6. The Hydrogenation of the Porphyrin Ligand

The π-electron system of the porphyrin ligand and the nitrogen-metal interaction in the plane have so far been considered in their entirety. The relative reactivities of the carbon centers (methine bridges, α and β positions of the pyrrole rings) will now be discussed. A suitable starting point for this discussion is an electron distribution *(20)*, which was first formulated by *Woodward*[54]. If one assumes that the pyrrole rings still lead an independent existence in the macrocyclic conjugation system of the metal-porphyrin complexes, in the sense that each strives to attain a stable sextet of electrons, then in the neutral porphyrin ligand, *i.e.* formally when no electrons are transferred from the metal to the porphyrin and no redox reaction has taken place on the porphyrin, the methine bridges are positively charged, and nucleophilic additions should take place more easily. On the other hand, if electrons are introduced from the central metal ion or by reduction of the ligand, this has practically no effect on the aromatic system of the pyrrole rings, but there should be a pronounced change in the electron density on the methine bridges. If the electron distribution *(20)* is regarded as qualitatively correct, the reactivities of the pyrrole carbon atoms should be similar to those in pyrrole, *i.e.* they should above all be accessible to electrophilic substitutions, whereas the reactivity of the methine bridges in porphyrin complexes with different metals should reflect the diversity that can be expected from these complexes according to their variable redox behavior (Fig. 10).



(20)

Theory and experiment are in qualitative agreement in showing that nucleophilic, electrophilic, and free-radical addition reactions in the porphyrin ligand all begin on the methine bridges. In the theoretical model proposed by *Fukui*, the coefficients of the frontier orbitals are used as a measure of the relative reactivities of the individual centers of a molecule; the approximation procedure of *Pariser*, *Parr*, and *Pople* was taken as the basis for their calculation in porphyrin. Maximum occupancies for the two frontier orbitals were found on the methine bridges in every case[55]. The chemical evidence for the special reactivity of the methine bridges consists mainly of the general observation that the primary attack of oxidizing and reducing agents and of nucleophilic agents usually occurs here and that electrophilic substitutions can also be carried out here if the partial positive charge on the bridge atoms in *(20)* is reduced by the introduction of a central metal ion. The principal hydrogenation reactions of porphyrin ligands will now be discussed.



On electrochemical reduction[43] or reaction with aromatic π-anions *e.g.* sodium diphenylketyl and sodium anthracenide[42], in aprotic solvents, metal-porphyrin complexes are reversibly converted into their π-monoanions *(18)* or π-dianions *(22)*, depending on the redox potential, with characteristic absorption spectra (Fig. 11). Protonation, *e.g.* with methanol, leads immediately to the formation of a new strong absorption band close to 800 nm (Fig. 11), which indicates

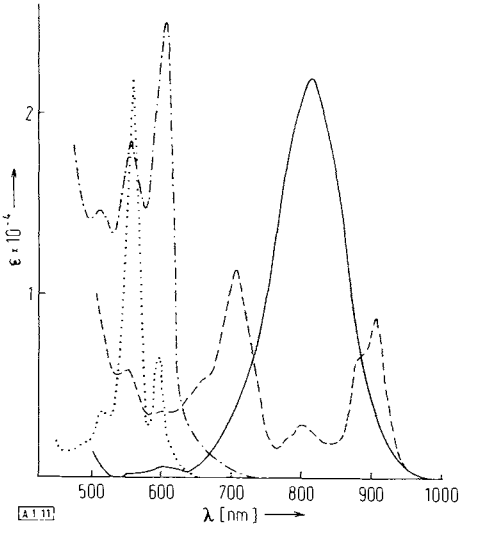


Fig. 11. Long-wave part of the spectra of tetraphenylporphinatozinc *(1)* (····), its π-radical-anion [type *(18)*] (– –), π-dianion [type *(22)*] (– · –), and phlorin radical-anion [type *(23)*] (— —). The spectra of the starting complex and of the dianion are surprisingly similar; the radical-anion *(18)* shows the typical broad free-radical band with long-wave maxima, and the intense phlorin band close to 800 nm is typical of tetrapyrrole pigment-metal complexes in which four pyrrole units are linked *via* three methine bridges and one methylene bridge.

the protonation of a methine bridge [(21), (23)]. On reoxidation of the ligand, the protons of the "phlorins" (21) and (23) are immediately liberated again, and the original porphyrin is formed once more.

Phlorins of the same type are also formed on photochemical reduction of porphyrins and their metal complexes[22, 54] but cannot always be detected, since metal-phlorin complexes are readily reduced further to porphodimethenes (24) with principal absorptions close to 500 nm[56].

The reversibility of the addition of hydrogen to the methine bridges has also been demonstrated in a cyclic process[57], which is similar in outline to the photosynthesis scheme of Figure 1. A mixture of a phlorin and a porphyrin in glycol undergoes conproportionation on irradiation to form two porphyrin radical-anions, which are converted back into the starting materials by a relatively slow dark reaction (Fig. 12).

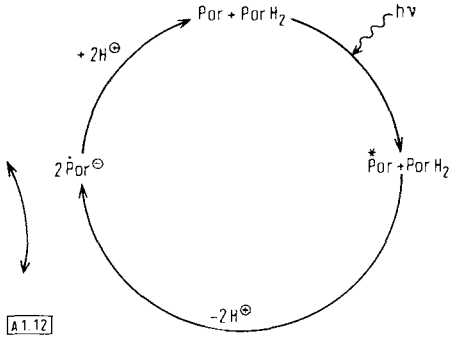
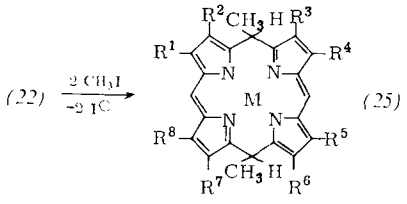


Fig. 12. Irradiation of equimolar quantities of a phlorin ($PorH_2$) and a porphyrin (Por) in glycerol leads to conproportionation into two porphyrin radical-anions, which disproportionate in a dark reaction into the starting materials (cf. Fig. 1). The double arrow on the left indicates that the radical-anions can oxidize or reduce other redox systems.

This cycle can be repeated several times. Instead of the formulated disproportionation of the radical-anions formed, an analogous reaction with other molecules is quite conceivable, a weak oxidizing agent taking over the oxidation to the original porphyrin and a weak reducing agent leading to the formation of the phlorin. The two substances reacting with the porphyrin radical would thus be converted into different oxidation states with no change in the composition of the porphyrin redox cycle, and light energy would thus have been converted into chemical energy. This reaction has not yet been demonstrated.

Reduction of porphyrins beyond the phlorin stage in the presence of protons leads first to porphodimethenes (24), which, like the phlorins, are very sensitive to air and are readily converted back into porphyrins. If methyl iodide is added to the solution instead of protonated solvents, however, the relatively stable α,γ-dimethylporphodimethenes (25) are obtained by "reductive methylation".

Buchler showed that the yield of (25) is strongly dependent on the nature of the central metal ion[58]. The yields are generally higher for metal ions with low electronegativities, where the porphyrin ligand itself is relatively rich in electrons, than for strongly electron-attracting metal ions. The nucleo-

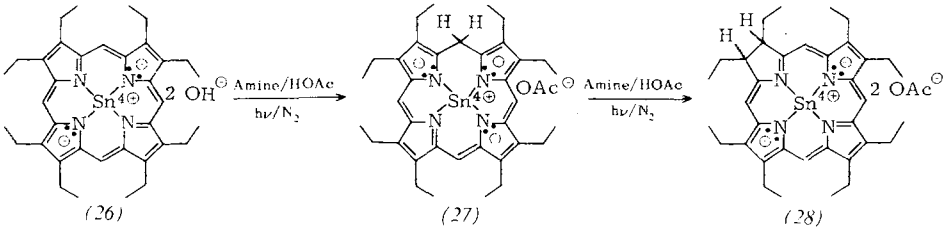


philicity of the methine groups can thus be strongly varied in the oxidation state of the porphyrindiyl π-dianion (22) by the use of different metal ions without affecting the point of attack of this addition reaction. This is in agreement with the model discussed at the beginning of this section. The fact that only the methine bridge situated opposite is attacked at first in the reduction of phlorins can be correlated with the results of model calculations[55], according to which the charge density in this position (1.09) is very much greater than on the neighboring bridges (0.92).

Finally, porphyrins can be reduced to colorless porphyrinogens[59], *e.g.* (4) and (9), in which all four methine bridges are hydrogenated, and which no longer form stable metal complexes. This reduction is still fully reversible by oxidizing agents, *e.g.* oxygen. Further catalytic hydrogenation leads to addition to the α-pyrrole carbon atoms, followed immediately by irreversible cleavage of the porphyrin macrocycle[60].

All hydrogenation experiments on porphyrins and their metal complexes thus confirm the model postulated at the beginning: the methine bridges readily enter into addition reactions, whereas the pyrrole rings do not react. The hydrogenation of β,β'-pyrrole double bonds in porphyrins is of special interest in connection with the synthesis of derivatives of chlorophyll (2). It can be achieved by the use of sterically hindered hydrogen carriers in strongly alkaline solution (*e.g.* diimine with KOH[63] or K_2CO_3[61], isoamyl alcohol with sodium[62]) or with the aid of special intramolecular rearrangements[53], which will not be discussed here. These and other preparative aspects of porphyrin chemistry and the related reactions of chlorins and corrin derivatives have recently been reviewed by *Inhoffen*[63] and *Smith*[64].

However, the direct rearrangement of a metal-phlorin derivative into a metal-chlorin derivative has also been observed in neutral solution in one case. This irradiation of porphinatotin(IV) derivatives (26) leads first to phlorins (27), which rearrange relatively rapidly and almost quantitatively into chlorins (28)[65] without the formation of porphodimethenes (24).

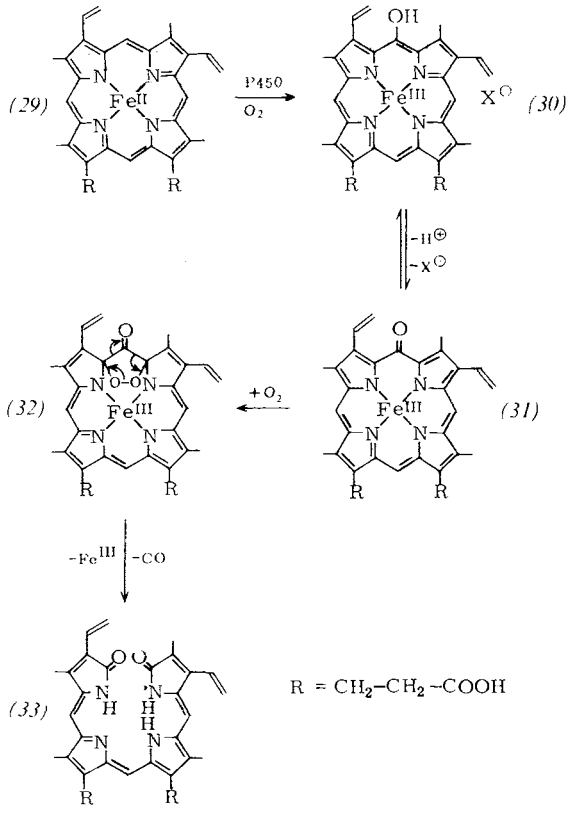


Out of 20 metal-porphyrin complexes used, the closely related porphinatogermanium(IV) was the only other that exhibited this reaction[65]. The strongly electron-attracting Sn^{IV} evidently polarizes the porphyrin ligand so strongly that even the β-pyrrole carbon atoms acquire a partial electropositive character and thus become easier to reduce. This agrees with the lengthening of the β,β'-pyrrole bond observed in X-ray investigations (porphinatonickel: 1.350 Å, porphinatotin(IV) 1.379 Å)[28]. It has recently been shown that chlorins can be converted into phlorins under strongly basic conditions[101]. A detailed review article of inorganic, organic, and biological studies on the reversible redox chemistry of the metalloporphyrin complex has recently been published[103].

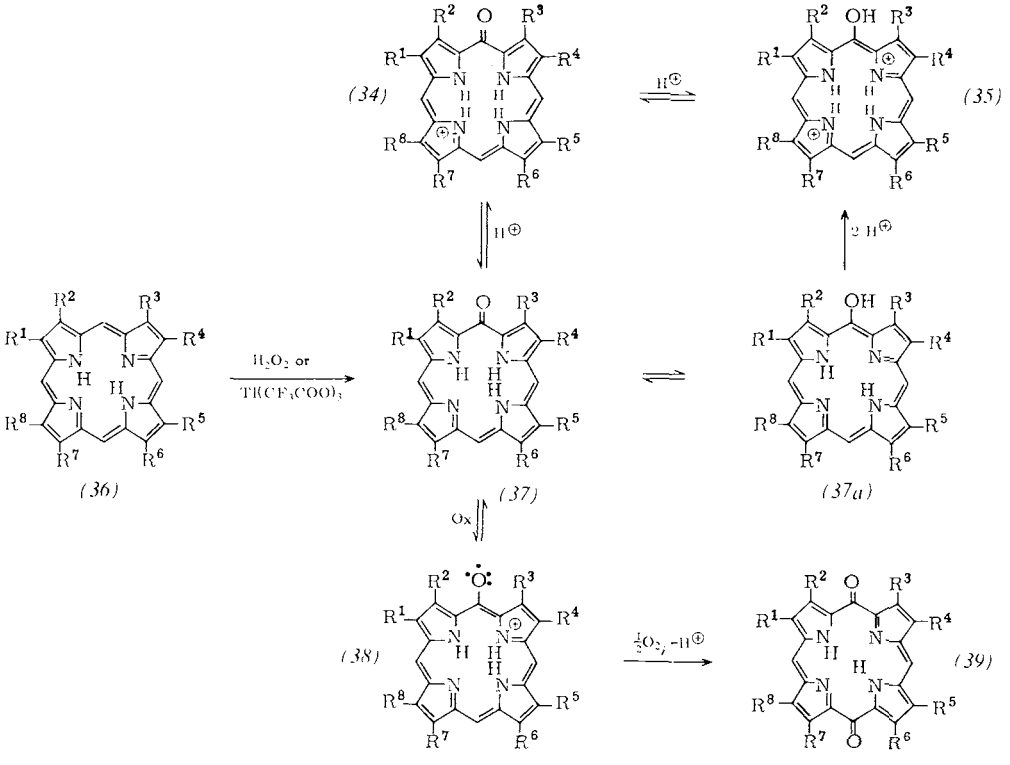
7. Reactions of the Porphyrin Ligands with Oxygen

The iron-porphyrin chromophore of hemoglobin and other heme proteins, is not excreted as such on biological degradation of the protein component, but is oxidatively degraded to biliverdin *(33)*, which is then reduced to the familiar bile pigments of the feces and urine[8, 23]. The primary formation of biliverdin presumably occurs in two stages. A cytochrome enzyme (P 450) first hydroxylates the α-methine bridge of the heme *(29)* to form the hydroxyheme *(30)*, which loses acid to establish an equilibrium with the analogous oxophlorin *(31)*. The latter then adds an oxygen molecule to the two neighboring α-pyrrole positions, possibly in a non-enzymatic step, to form *(32)*; like the hydrogenation of these positions, this immediately leads to opening of the porphyrin macrocycle and also to loss of a molecule of carbon monoxide[66, 67, 102] and the central iron atom[110].

The primary occurrence of the enzymatic reaction *(29)*→*(30)* is probable on the basis of different experiments carried out independently by two research groups. By planned inhibition experiments in the oxidation of heme by liver homogenates



and oxygen, *Schmid et al.*[9] demonstrated that a P 450 cytochrome is involved; this cytochrome is known to catalyze (probably exclusively) hydroxylations with molecular oxygen. *Kenner et al.*[110] synthesized α- and β-hydroxymesoheme, and showed that only the "natural" α-isomer was degraded to biliverdin by liver homogenates. The second reaction, *(31)*→*(32)* has so far remained hypothetical, but agrees with existing knowledge about the specific reactivity of the porphyrin ligand, and also readily explains the physiological remo-



val of carbon monoxide, which has been conclusively demonstrated[67,68]; this reaction can therefore also be regarded as very probable.

Hydroxyporphyrins can be prepared in reasonable yields by oxidation of porphyrins such as *(36)* or of metal-porphyrin complexes[63,68] with hydrogen peroxide. However, the best method is the oxidation of porphyrins with thallium(III) salts, which gives almost quantitative yields[69].

Hydroxyporphyrins *(37a)* probably exist in neutral solution in the tautomeric form of the oxophlorins *(37)*; this was deduced mainly from an anomalous absorption spectrum (Fig. 13) and a strong IR absorption close to 1600 cm^{-1}[79,74].

Protonation, deprotonation, and metal complex formation lead to porphyrin-like spectra; this is the basis for the formulation *e.g.* of the equilibria *(37)*⇌*(34)*, *(34)*⇌*(35)*, and *(30)*⇌*(31)*. Easy interconversion of porphyrin and phlorin structures is therefore observed here just as for the "true" phlorins, which are formed by hydrogenation, and is a good indication that there are only slight energy differences between the macrocyclic "aromatic" conjugation system of the porphyrins and the polyene-like conjugation of the phlorins.

Neutral oxophlorins *(37)* can be very readily oxidized to stable π-radicals *(38)*[71]; the equivalence potential of *(37)*, R^1—R^8 = C_2H_5, with a value of −50 mV (SCE), is about 700 mV lower than that of octaethylporphin itself. The findings can probably be generalized as follows: Phlorins and oxophlorins are more easily oxidized and reduced than the analogous porphins. The resonance stabilization energies of the two systems are approximately equal.

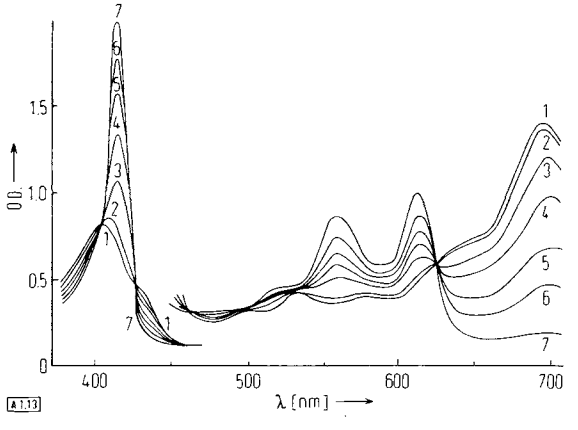


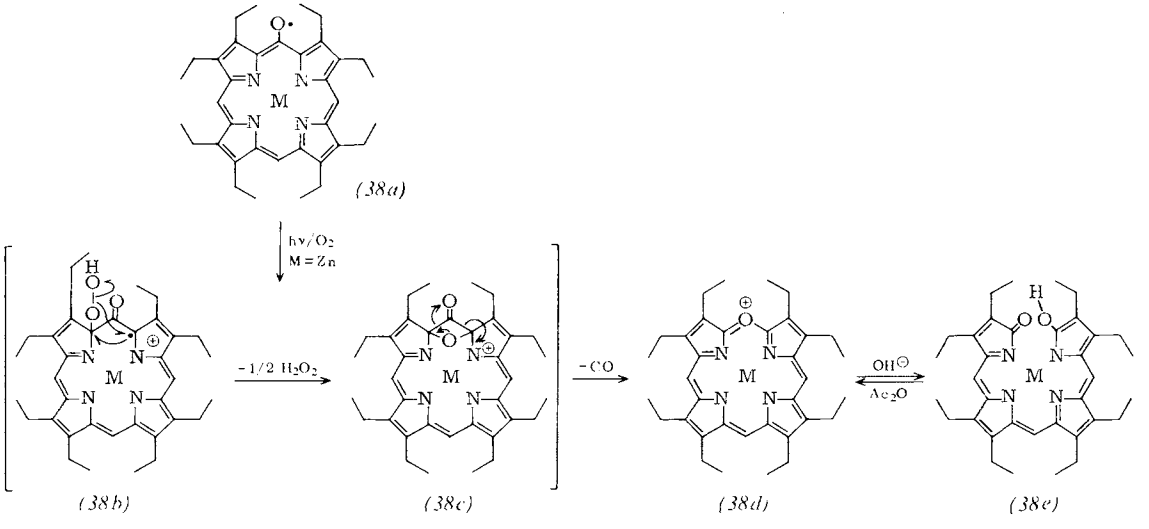
Fig. 13. Spectrophotometric titration of the octaethyloxophlorin cation *(34)*, R^1-R^8 = C_2H_5, in chloroform to form the porphyrin dication *(35)* [70]. This titration is one indication of the easy and reversible conversion of the conjugation system of porphyrins into that of phlorins (cf. Figs. 5 and 11). The left-hand part of the figure was recorded in a 1 mm cell, and the right-part in a 10 mm cell.

It must also be mentioned that phlorin radicals [*e.g. (21), (38)*] are very much less stable toward irreversible additions than the metal-porphin radicals [*e.g. (18), (19)*]. For example, the oxophlorin radical *(38)* reacts rapidly and almost quantitatively with molecular oxygen to form the quinone-like α,γ-dioxoporphodimethene *(39)*; this reaction is again exactly analogous to the results of the hydrogenation of *(21)* to *(24)*, though the influence of the central metal ions on the addition of oxygen has not yet been investigated. A series of photochemical reactions of the oxophlorin radical *(38a)* have recently been studied. They lead, *inter alia*, to an oxaporphyrin *(38d)*, which is formed in good yields and can be quantitatively and reversibly converted into the biliverdin *(38e)*[102]. The reaction sequence *(38a)*→*(38e)* is a plausible alternative to *(31)*→*(33)*. The singlet oxygen of the photo-oxygenation of the zinc complex *(38a)* would then correspond to the peroxide anion of the oxyhemoglobin in the natural process.

Oxidation of a porphyrin under drastic conditions leads initially, before the macrocycle is degraded, to reaction of all four methine bridges without attack on the pyrrole rings. The reaction of porphyrins with lead dioxide gives almost quantitative yields of the stable xanthoporphyrinogens *(40)* (*xanthos* = yellow), which crystallize well[72,73]; this reaction is analogous to the porphyrinogen formation on hydrogenation of porphyrins, and again demonstrates the particular stability of the pyrrole units.

However, the reaction proceeds quite differently if the starting porphyrin contains vinyl groups as substituents, as in the case of protoporphyrin. The reaction of these unsaturated side chains with lead dioxide results in irreversible, undefined destruction of the macrocycle. Xanthoporphyrinogens react with reducing agents, *e.g.* sodium amalgam, to give the starting porphyrins again in good yields, *i.e.* the oxidative porphyrinogen formation is also reversible.

In addition to the formation of oxophlorins *(37)* from porphyrins *(36)*, a second way in which the porphyrin ligand can react with oxygen has also been observed. If metal-por-



(38a) *(38b)* *(38c)* *(38d)* *(38e)*

phyrin complexes with low porphyrin ligand oxidation potentials (*e.g.* octaethylporphinatomagnesium) are exposed to visible light in the presence of air in benzene solution, spectroscopic examination shows that the porphyrin ligand is quantitatively converted into a chromophore with an intense absorption band above 800 nm (Fig. 14)[74-77]. This reaction

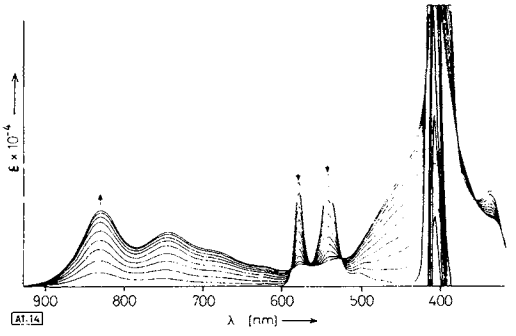
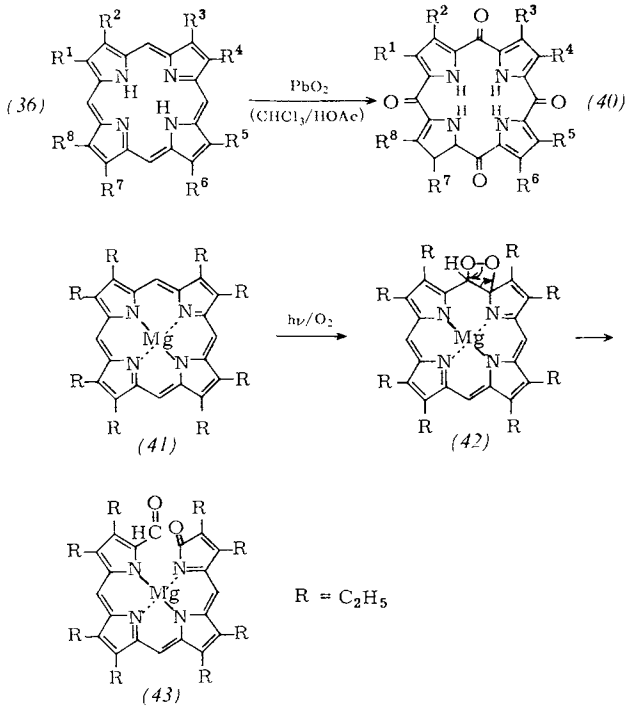


Fig. 14. The reaction *(41)*→*(43)*, such as occurs on irradiation of octaethylporphinatomagnesium in benzene in the presence of air, followed spectrophotometrically [75–77].

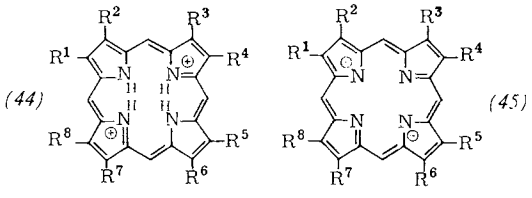
proceeds perfectly uniformly and no intermediates with lifetimes of more than 10 s occur. The quantum yield is of the order of 10^{-3}; in the underlying reaction an open-chain magnesiumformylbiliverdin complex *(43)*, which is extremely readily hydrolyzed, is formed *via* the postulated stage of a short-lived peroxide, possibly *(42)*[77,78].

As was indicated above, this reaction can be carried out only if the porphyrin ligand has a low oxidation potential, *i.e.* if it carries the highest possible partial negative charge. This observation is an excellent example of a general pattern of the reactivity of the porphyrin ligand in its metal complexes: Chelates with low potentials in the one-electron oxidation described above react readily with molecular oxygen, but are very difficult to hydrogenate (extreme example: magnesium-porphyrin complexes). Conversely, metal-porphyrin complexes with high porphyrin ligand oxidation potentials



do not react with oxygen, or even *e.g.* with elementary bromine in extreme cases, but are very easy to hydrogenate (most pronounced in tin(IV)-porphyrin complexes)[65]. Between the two extremes there is a close succession of metal-porphyrin complexes with graded reactivities corresponding to Figure 10.

Qualitatively similar relationships between reactivity and redox potentials have also been found for the protonated porphyrins *(44)* and the deprotonated porphyrins *(45)*: for example, the cations *(44)* can be readily hydrogenated photochemically to phlorins[22] and porphodimethenes[22,79], while anions of the type *(45)* can be quantitatively oxygenated in a reaction analogous to *(41)*⇌*(43)*[80,81], but in this case subsequent solvolytic reactions occur immediately in the strongly alkaline solution that is necessary for the formation of *(45)*. Substituents on the methine bridges or on the β-pyrrole carbon atoms also influence reactivity and redox potentials. Substitution of a methine proton by a nitrile group increases *e.g.* the oxidation potential of the porphyrin ligand by about 250 mV[82].



8. The Polyene Character of Phlorins

The physical and chemical properties of the phlorins can be rationalized in the same way as for the porphyrins in Section 3. While singly degenerate frontier orbitals were regarded as related to the aromatic behavior of the porphyrins (electronic spectrum, magnetic ring current, formation of stable radicals, *etc.*), the known properties of the phlorins (no bands differing in intensity by orders of magnitude in the electronic spectrum; no ring current effect; few stable radicals, which tend to undergo irreversible addition reactions) point to their polyene character. The metal complexes of biliverdin behave similarly[77,81].

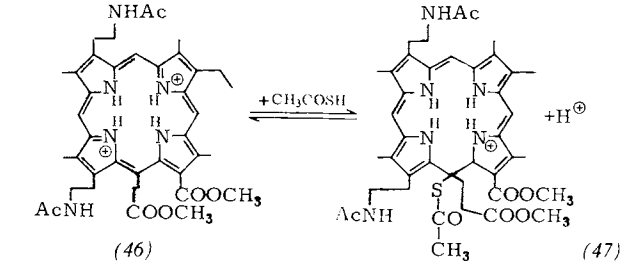
Similar transitions are found for benzene and its derivatives (Wheland and Meisenheimer complexes), but the polyene-like addition compounds here can often be studied only under extreme conditions (interception at low temperature, superacids, *etc.*), whereas phlorins are readily obtainable.

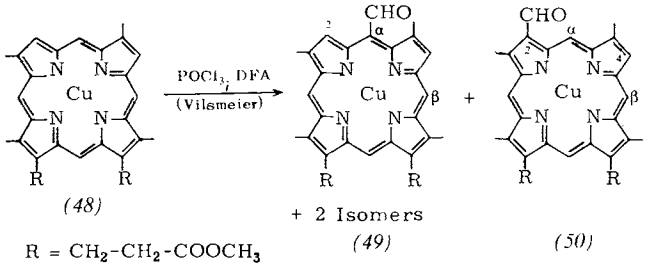
After the introduction of the central metal ions into the oxophlorins *(37)*, it should also be possible to study the influence of inductive effects on the stability of the macrocyclic benzene-like conjugation system. Investigations of this type on the porphyrin-phlorin equilibria are still in their early stages, mainly because of our fragmentary knowledge of the properties of the phlorins and their metal derivatives, and are numbered among the fascinating aspects of metal-porphin chemistry.

9. Other Electrophilic and Nucleophilic Reactions on the Porphyrin Ligand

The reaction patterns proposed for reversible and irreversible redox reactions of the porphyrin ligand are also valid for

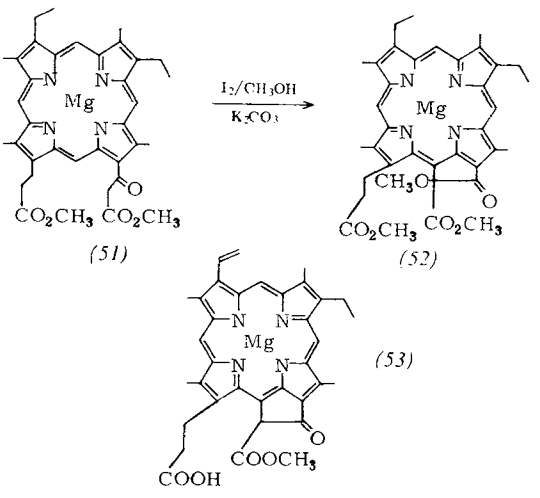
other chemical reactions: positively charged porphyrin ligands, *e.g.* the dication *(46)*, readily undergo nucleophilic reactions, *e.g.* *(46)*⇌*(47)*[54], whereas metal-porphyrin complexes in which the porphyrin ligand carries a partial negative charge, *e.g.* *(48)* react more readily with electrophilic agents. Copper and nickel porphyrins have proved to be the best metal complexes for electrophilic substitutions, *e.g.* the Vilsmeier formylation, since the porphyrin ligand has a sufficiently negative partial charge to compensate for the inherent partial positive charge on the methine bridges [see *(20)*], but the metal complexes are also sufficiently stable toward acids to withstand the conditions of electrophilic substitutions (usually strongly acidic solutions); this would not be so *e.g.* for magnesium- or zinc-porphyrin complexes, which are themselves more reactive. As expected, the dimethyl ester of deuterioporphinatocopper(II) *(48)* is formylated with roughly equal probabilities on the methine bridges [*e.g.* *(49)*] and on the β-pyrrole carbon atom [*e.g.* *(50)*][83]. Many other electrophilic substitutions on the porphyrin ring proceed with very good yields, *e.g.* nitration[84] and chlorination[85], but no new points of view would result from the discussion of these reactions.



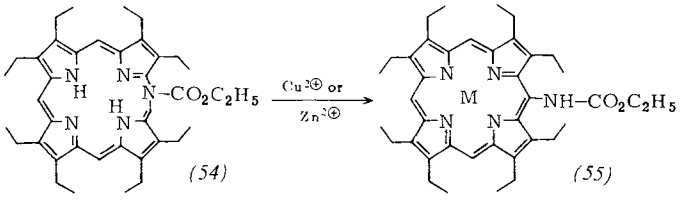


As was shown in Section 5, the presence of magnesium as the central metal ion makes it easy to oxidize the porphyrin ligand to the radical-cation, and this specific reactivity is probably also utilized in the biosynthesis of chlorophyll. *Kenner et al.*[89] were able to show that the magnesium complex of the 6-β-ketopropionic ester *(51)* can be cyclized to form a protochlorophyll analog *(52)* if *(51)* is oxidized to the π-radical-cation with iodine in methanol in the presence of potassium carbonate. Other reaction conditions did not lead to substitutions of this type; it seems reasonable to conclude that the *in-vivo* synthesis of the carbocycle in protochlorophyllide *(53)* proceeds in a similar manner.

Another aspect of metal-porphyrin chemistry is the tendency of the metal ion to eliminate disturbances of the square-planar ligand field. This effect undoubtedly plays a part in the reactions of metal-phlorin complexes *(21)*, which readily react further to form porphodimethenes *(24)*, whose ligand field is similar to that of the porphyrins, and was recently claimed



by *Grigg*[94] to be responsible for the extreme catalytic activity of copper or zinc ions in the ring contraction *(54)*→*(55)*.



Other reactions of the porphyrin ligand are discussed in detail in the reviews by *Inhoffen*[63] and *Smith*[64].

10. π-Complexes with Metal-Porphyrin Complexes

Metal-porphyrin complexes form definite π complexes with other aromatic molecules or self-associates, some of which have surprising properties. This association type of reaction is important to the biological activity of the metal-porphyrin complexes, since the electron and energy transport in redox chains and light-accumulating aggregates is probably connected with interactions of this type. For example, the photosynthesis reaction of the cycle in Figure 1 can also be symbolized by a light-induced charge transfer of the form

$$\text{Chl A} \overset{h\nu}{\rightleftharpoons} \text{Chl}^{\oplus}\ \text{A}^{\ominus}$$

the reverse reaction then occurring by oxidation of the electron acceptor radical $A^{\ominus}$ by a weak oxidizing agent and reduction of the chlorophyll radical-cation $Chl^{\oplus}$ by a weak reducing agent.

Molecular compounds of the porphyrins have been systematically investigated by *H. Fischer*[85] and *Mauzerall*[86]; the 1:1 or 1:2 complexes normally formed by aromatic compounds with nitrophenols, nicotinic acid, *etc.* were generally detected both in solution and in the crystalline phase. The spectroscopic effects of the complex formation usually consist of relatively slight shifts of the absorption maxima together with band broadening[86], which also occur in the self-association *e.g.* of chlorophyll[87].

Shifts of the methine proton NMR signals have also been used for the detailed elucidation of the structure of chlorophyll associates in solution[87], and have been attributed to the

addition of the magnesium ion to the carbonyl group of the carbocycle of a neighboring molecule.

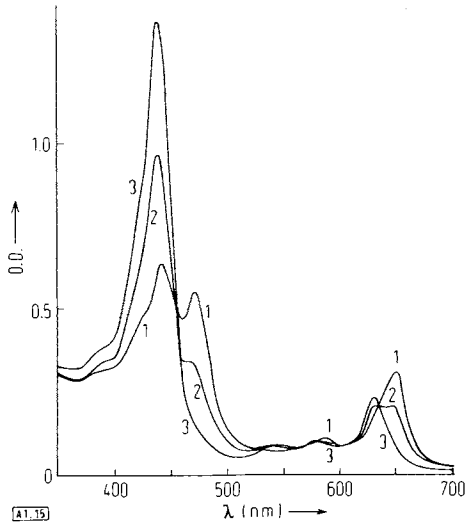


Fig. 15. The spectrum 1 of protochlorophyllide *(53)* in apolar solvents has a maximum at 650 nm and a split Soret band in the near UV. Addition of methanol leads to cleavage of the associate responsible, and spectrum 3 with an intense, sharp UV absorption appears; this corresponds to monomeric *(53)*. Similar changes in the spectrum of protochlorophyllide *(53)* are also observed *in vivo* in etiolated plants. Spectrum 2 corresponds to a mixture of aggregated and monomeric molecules.

Three unusual molecular aggregates of metal-porphyrin complexes will now be discussed briefly. *B. Ke*[88] found that protochlorophyllide *(53)* in apolar solvents forms an associate whose long-wave absorption band is displaced by almost 20 nm in relation to that of the monomer, and whose Soret band is split and strongly broadened (Fig. 15). This spectrum corresponds exactly to that of the "active" protochlorophyllide in etiolated plants, which is immediately hydrogenated to chlorophyll on exposure to light. The spectrum of the monomeric protochlorophyllide, on the other hand, agrees with that of the inactive, unreducible protochlorophyllide of the plants. This *in-vitro* experiment thus indicates that the protochlorophyllide in the plant is initially bonded to a hydrophobic matrix, probably a protein[95], where it forms a self-associate, and can only then be hydrogenated.

Wang[90,91] recently showed that chlorophyll reacts with flavins in solution to form a molecular complex with an absorption maximum at 700 nm, which is reversibly bleached on exposure to visible light. An EPR signal appears at the same time. This reaction is fully reversible in the dark, and may be regarded as a further model for the light-induced electron transfer of the photosynthesis, in which the reversible bleaching of a "P 700" is also observed in the photochemical system I[92].

The molecular complexes described so far are based on the usual weak interactions of π-electronic systems and side chains (ionic bonds, van der Waals forces, *etc.*)[86]. The bonding enthalpy of these complexes is probably less than ≈ 3 kcal/mol in every case[86]. Much stronger bonds have been observed on dimerization of radical-cations. The best defined complex of this type is the diamagnetic dimer of the octaethylporphinatozinc radical-cation, whose high enthalpy of formation of 17.5 kcal/mol and extremely intense charge-transfer band (oscillator strength 0.75) (Fig. 16) at 930 nm led to the formulation of a novel π-π' bond type, in which a new singlet ground state with a low energy is formed by multicenter overlapping and pairing of the electrons in the half-filled outermost orbitals[93]. π-π' bonds of this type between two similar radicals have also been observed for other aromatic free radicals (*e.g. Wurster*'s blue), but the formation enthalpies are once more in the region of weak interactions, and are about one order of magnitude lower than in the case under discussion at present[96].

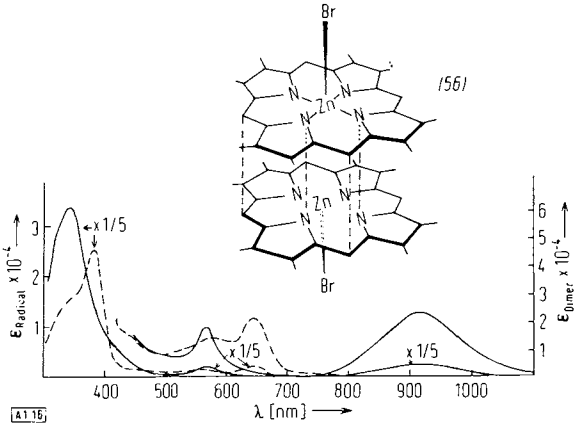


Fig. 16. Electronic spectrum of the octaethylporphinatozinc radical-cation (– – –) and its diamagnetic π-π' dimer *(56)* (——) (as counterion in each case) with an intense charge-transfer band at 930 nm. (Only the skeleton of the dimer is shown.)

11. Outlook

Most of what is known about the reactivity of the porphyrin ligand has been discovered in the course of the last twelve years. The discovery of the phlorins and the elucidation of their structure, the detailed investigation of the metal-nitrogen bond and its retroaction on the π-electron system, the experimental and theoretical proof of the degeneracy of the outermost orbitals, the discovery of the metal-porphyrin radicals and the conclusive detection of chlorophyll radicals in a light reaction of the photosynthesis, the contributions to our knowledge of the photochemical and biological degradation of porphyrins and of the formation of protochlorophyll can be mentioned as special milestones in this recent development, which began with *Woodward*'s synthesis of chlorophyll. Many of these topics contain other interesting problems for future experimental and theoretical studies. Thus 15 years after the discovery of phlorins and oxophlorins *in vitro*, their occurrence in biological systems has not yet been directly detected, though they very probably occur in some reactions of the biosynthesis of metal-porphyrin complexes, and should be easy to detect on the basis of their intense absorption in the near infrared; there is no theoretical model that is even approximately satisfactory for the strong influence of the central metal ions on the reactivity of the porphyrin ligand, and as a final concrete example of an unsolved problem in porphyrin chemistry, we can mention the preparation of the as yet hypothetical oxophlorin peroxides such as *(32)* or *(38c)* and the detailed elucidation of the decarbonylation to biliverdin *(33)* in which two carbon-carbon bonds and a peroxide bridge are broken. If the scheme *(29)*→*(33)* or *(38a)*→*(38e)* should also be confirmed biochemically, new

pathways would also be opened up for clinical research on heme degradation.

On the whole, interest is currently shifting more and more toward problems of the weak or catalytic interactions in which the porphyrins participate. Important examples are the formation and reactivity of charge transfer complexes, the electron distribution in oxyhemoglobin, the activation of molecular oxygen with metal-porphyrin systems for catalytic hydroxylations and oxygenations of hydrocarbons, and the transport of electrons through membranes containing metal-porphyrin complexes (see *e.g.*[97,98]). All these problems are concerned with the ability of the porphyrin ligand to give up or even "nearly" to give up electrons, a property that also determines the "normal" chemistry of the fascinating macrocycle that has been the subject of this progress report.

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[1] *M. Klingenberg* in *T. P. Singer*: Biological Oxidations. Interscience, New York 1968, p. 3ff.

[2] *E. Antonini* and *M. Brunori*: Hemoglobin and Myoglobin in their Reactions with Ligands. North-Holland Publ. Co., Amsterdam 1971, p. 235ff.

[3] *V. Ullrich*, Angew. Chem. *84*, 689 (1972); Angew. Chem. internat. Edit. *11*, 701 (1972).

[4] *B. Kok* in *J. Bonner* and *J. E. Varner*: Plant Biochemistry. Academic Press, New York 1965.

[5] *B. Commoner, J. Townsend*, and *G. Pake*, Nature *174*, 689 (1954).

[6] *D. Kohl* in *H. M. Swartz, J. R. Bolton*, and *D. C. Borg*: Biological Applications of ESR. Wiley, New York 1972, p. 213ff.

[7] *H. Fischer* and *H. Orth*: Die Chemie des Pyrrols II, 1. Akademische Verlagsgesellschaft, Leipzig 1937, p. 697ff.

[8] *R. Lemberg* and *J. W. Legge*: Hematin Compounds and Bile Pigments. Interscience, New York 1949, p. 453ff.

[9] *R. Tenhunen, H. Marver, N. R. Pimstone, W. F. Trager, D. J. Cooper*, and *R. Schmid*, Biochemistry *11*, 1716 (1972).

[10] *T. Kondo, D. C. Nicholson, A. H. Jackson*, and *G. W. Kenner*, Biochem. J. *121*, 601 (1971).

[11] *R. G. Clayton* in *L. P. Vernon*, and *G. R. Seely*: The Chlorophylls. Academic Press, New York 1966, p. 609ff.

[12] *W. T. Simpson*, J. Chem. Phys. *17*, 1218 (1949).

[13] *M. Gouterman*, J. Chem. Phys. *30*, 1139 (1959).

[14] *C. Weiss, H. Kobayashi*, and *M. Gouterman*, J. Mol. Spectrosc. *16*, 415 (1965).

[15] *W. Küster* and *P. Deihle*, Hoppe-Seylers Z. Physiol. Chem. *82*, 463 (1913).

[16] *W. Siedel* and *F. Winkler*, Liebigs Ann. Chem. *554*, 162 (1943).

[17] *H. H. Inhoffen, J.-H. Fuhrhop, H. Voigt*, and *H. Brockmann jr.*, Liebigs Ann. Chem. *695*, 133 (1966).

[18] *A. Baeyer*, Ber. Deut. Chem. Ges. *19*, 2184 (1886).

[19] *A. H. Corwin, A. B. Chivvis*, and *C. B. Storm*, J. Org. Chem. *29*, 3702 (1964).

[20] *D. Mauzerall*, J. Amer. Chem. Soc. *82*, 2605 (1960).

[21] *A. D. Adler, L. Sklar, F. R. Longo, J. D. Finarelli*, and *M. G. Finarelli*, J. Heterocycl. Chem. *5*, 669 (1968).

[22] *D. Mauzerall*, J. Amer. Chem. Soc. *82*, 2601 (1960).

[23] *S. Granick* and *D. Mauzerall* in *D. M. Greenberg*: Metabolic Pathways. Vol. II. Academic Press, New York 1961, p. 526ff.

[24] *J. Lascelles*: Tetrapyrrole Biosynthesis and its Regulation. Benjamin, New York 1964.

[25] *W. Kuhn*, Kolloid-Z. *68*, 2 (1934).

[26] Numerous examples in [7].

[27] *S. Krol*, J. Org. Chem. *24*, 2065 (1959).

[28] *J. L. Hoard*, Science *174*, 1295 (1971).

[29] *C. D. Hodgman*: Handbook of Chemistry and Physics. Chem. Rubb., Cleveland 1962, p. 3511 and 3512.

[30] *M. Malley, G. Feher*, and *D. Mauzerall*, J. Mol. Spectrosc. *26*, 320 (1968).

[31] *G. W. Canters, J. van Egmond, T. J. Schaafsma, I. Y. Chan, W. G. van Dorp*, and *J. H. van der Waals*, Ann. N. Y. Acad. Sci. *206*, 711 (1973).

[32] *J.-H. Fuhrhop* and *D. Mauzerall*, J. Amer. Chem. Soc. *90*, 3875 (1968); *91*, 4174 (1969).

[33] *J. F. M. Oth, H. Baumann, J. M. Gilles*, and *G. Schröder*, J. Amer. Chem. Soc. *94*, 3498 (1972).

[34] *L. M. Jackman* and *S. Sternhell*: Application of NMR Spectroscopy. Pergamon, Oxford 1969, p. 96ff.

[35] *P. Hambright*, Coord. Chem. Rev. *6*, 247 (1971).

[36] *J. Buchler, L. Puppe, K. Rohbock*, and *H. H. Schneehage*, Ann. N. Y. Acad. Sci. *206*, 116 (1973).

[37] *K. Kadish, D. G. Davis*, and *J.-H. Fuhrhop*, Angew. Chem. *84*, 1072 (1972); Angew. Chem. internat. Edit. *11*, 1014 (1972).

[38] *S. Sailendra* and *N. G. Podder*, J. Indian Chem. Soc. *47*, 39 (1970).

[39] *F. A. Cotton* and *G. Wilkinson*: Anorganische Chemie. Verlag Chemie, Weinheim 1967.

[40] *E. Heilbronner* and *H. Bock*: Das HMO-Modell und seine Anwendung. Vol. 2. Verlag Chemie, Weinheim 1970, p. 384.

[41] *J.-H. Fuhrhop, K. Kadish*, and *D. G. Davis*, J. Amer. Chem. Soc. *95*, 5140 (1973).

[42] *G. L. Closs* and *L. E. Closs*, J. Amer. Chem. Soc. *85*, 818 (1963).

[43] *G. Peychal-Heiling* and *G. S. Wilson*, Anal. Chem. *43*, 545, 550 (1971).

[44] *J. Fajer, D. C. Borg, A. Forman, D. Dolphin*, and *R. H. Felton*, J. Amer. Chem. Soc. *92*, 3451 (1970).

[45] *J.-H. Fuhrhop*, Z. Naturforsch. *25b*, 255 (1970).

[46] *M. Zerner* and *M. Gouterman*, Theor. Chim. Acta *4*, 44 (1966).

[47] *L. J. Boucher*, Coord. Chem. Rev. *7*, 289 (1972).

[48] *E. B. Fleischer* and *T. S. Srivastava*, J. Amer. Chem. Soc. *92*, 5518 (1970).

[49] *C. Weiss*, J. Mol. Spectrosc. *44*, 37 (1972).

[50] *D. Dolphin, R. H. Felton, D. C. Berg*, and *J. Fajer*, J. Amer. Chem. Soc. *92*, 743 (1970).

[51] *E. B. Fleischer*, Accounts Chem. Res. *3*, 165 (1970).

[52] *D. Mauzerall* and *S. Granick*, J. Biol. Chem. *232*, 1141 (1958).

[53] *R. B. Woodward*, Angew. Chem. *72*, 651 (1960).

[54] *R. B. Woodward*, Ind. Chim. Belge *1962*, 1293.

[55] *J. V. Knop* and *J.-H. Fuhrhop*, Z. Naturforsch. *25b*, 729 (1970).

[56] *A. V. Umrikhina, G. A. Yusupova*, and *A. A. Krasnovskii*, Dokl. Akad. Nauk SSSR *175*, 1400 (1967).

[57] *D. Mauzerall* and *G. Feher*, Biochim. Biophys. Acta *88*, 658 (1964).

[58] *J. W. Buchler* and *L. Puppe*, Liebigs Ann. Chem. *740*, 142 (1970).

[59] *W. Küster*, Hoppe-Seylers Z. Physiol. Chem. *82*, 467 (1912).

[60] *R. A. Chapman, M. W. Roomi, T. C. Morton, D. T. Krajcarski*, and *S. F. MacDonald*, Can. J. Chem. *49*, 3544 (1971).

[61] *H. W. Whitlock, R. Hanauer, M. Y. Oester*, and *B. K. Bower*, J. Amer. Chem. Soc. *91*, 7485 (1969).

[62] *U. Eisner*, J. Chem. Soc. *1957*, 3461.

[63] *H. H. Inhoffen, J. W. Buchler*, and *P. Jäger*, Fortschr. Chem. Org. Naturst. *26*, 785 (1968).

[64] *K. M. Smith*, Quart. Rev. Chem. Soc. *25*, 31 (1971).

[65] *J.-H. Fuhrhop* and *T. Lumbantobing*, Tetrahedron Lett. *1970*, 2815.

[66] *T. Sjöstrand*, Acta Physiol. Scand. *26*, 338 (1950).

[67] *R. F. Troxler, A. Brown, R. Lesler*, and *P. White*, Science *167*, 192 (1970).

[68] *R. Bonnett* and *M. J. Dimsdale*, J. C. S. Perkin I *1972*, 2540.

[69] *K. M. Smith*, Chem. Commun. *1971*, 540.

[70] *A. H. Jackson, G. W. Kenner*, and *K. M. Smith*, J. Chem. Soc. *C 1968*, 302.

[71] *J.-H. Fuhrhop, S. Besecke*, and *J. Subramanian*, J. C. S. Chem. Comm. *1973*, 1.

[72] *H. Fischer* and *A. Treibs*, Liebigs Ann. Chem. *451*, 209 (1927).
[73] *H. H. Inhoffen, J.-H. Fuhrhop*, and *F. v. d. Haar*, Liebigs Ann. Chem. *700*, 92 (1966).
[74] *J. Barrett*, Nature *215*, 733 (1967).
[75] *J.-H. Fuhrhop* and *D. Mauzerall*, Photochem. Photobiol. *13*, 453 (1971).
[76] *P. Wasser* and *J.-H. Fuhrhop*, Ann. N. Y. Acad. Sci. *206*, 533 (1973).
[77] *P. Wasser*, Dissertation, Technische Universität Braunschweig 1973.
[78] *A. V. Umrikhina, G. A. Yusupova*, and *A. A. Krasnovskii*, Dokl. Akad. Nauk SSSR *175*, 1400 (1967).
[79] *H. Fischer* and *K. Herrle*, Hoppe-Seylers Z. Physiol. Chem. *251*, 85 (1938).
[80] *J.-H. Fuhrhop* and *A. Salek*, unpublished.
[81] *J.-H. Fuhrhop*, unpublished.
[82] *H. H. Inhoffen, H. Brockmann jr.*, and *K. M. Bliesener*, Liebigs Ann. Chem. *730*, 173 (1969).
[83] *R. Bonnett* and *G. F. Stephenson*, J. Org. Chem. *30*, 2891 (1965).
[84] *R. Bonnett, I. A. D. Gale*, and *G. F. Stephenson*, J. Chem. Soc. *C 1966*, 1600.
[85] See Ref. [7], p. 612.
[86] *D. Mauzerall*, Biochemistry *4*, 1801 (1965).
[87] *J. J. Katz, G. L. Closs, F. C. Pennington, M. R. Thomas*, and *H. H. Strain*, J. Amer. Chem. Soc. *85*, 3809 (1963).
[88] *B. Ke* and *C. J. Seliskar*, Biochim. Biophys. Acta *153*, 685 (1968).
[89] *M. T. Cox, T. T. Howarth, A. H. Jackson*, and *G. W. Kenner*, J. Amer. Chem. Soc. *91*, 1232 (1969).
[90] *S. J. Tu, Y. J. Tan*, and *J. H. Wang*, Bioinorg. Chem. *1*, 79 (1971).
[91] *J. H. Wang*, Accounts Chem. Res. *3*, 90 (1970).
[92] *A. Müller, B. Rumberg*, and *H. T. Witt*, Proc. Roy. Soc. (London) *157 B*, 313 (1963).
[93] *J.-H. Fuhrhop, P. Wasser, D. Riesner*, and *D. Mauzerall*, J. Amer. Chem. Soc. *94*, 7996 (1972).
[94] *R. Grigg*, J. Chem. Soc. *C 1971*, 3664.
[95] *N. K. Boardman* in *L. P. Vernon* and *G. R. Seely*: The Chlorophylls. Academic Press, New York 1966, p. 437.
[96] *K. H. Hausser* and *N. N. Murrell*, J. Chem. Phys. *27*, 500 (1957).
[97] *D. Mauzerall*, Nature *224*, 690 (1969).
[98] *H. W. Trissl* and *P. Läuger*, Biochim. Biophys. Acta *282*, 40 (1972).
[99] *J. Fajer, D. C. Borg, A. Forman, D. Dolphin*, and *R. H. Felton*, J. Amer. Chem. Soc. *95*, 2741 (1973).
[100] *L. Spaulding, P. G. Eller, J. A. Bertrand*, and *R. H. Felton*, J. Amer. Chem. Soc. *96*, 982 (1974).
[101] *H. W. Whitlock* and *M. Y. Oester*, J. Amer. Chem. Soc. *95*, 5738 (1973).
[102] *S. Besecke* and *J.-H. Fuhrhop*, Angew. Chem. *86*, 125 (1974); Angew. Chem. internat. Edit. *13*, 150 (1974).
[103] *J.-H. Fuhrhop*, Struct. Bond. *18*, in press.

COMMUNICATIONS

The First π-Diphenylketene-Carbonyl-Transition Metal Complexes

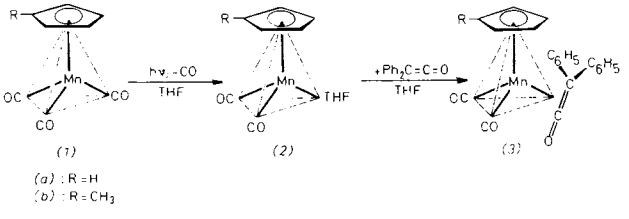
By *Wolfgang Anton Herrmann*[*]

The known reactions of ketenes with carbonyl-transition metal complexes result in deoxygenation and/or decarbonylation of the ketene and usually yield polynuclear metal derivatives[1]. On the other hand, catalytically active compounds of heavy metals are becoming increasingly important in ketene chemistry[2]. The first carbonyl-transition metal complexes containing the structurally intact diphenylketene moiety as ligand have now been synthesized.

Reaction of the THF complexes *(2a)* and *(2b)*, generated photochemically from *(1a)* and *(1b)* respectively, with diphenylketene in a molar ratio of 1:1 affords high yields of dicarbonyl(cyclopentadienyl)(diphenylketene)manganese *(3a)* and dicarbonyl(methylcyclopentadienyl)(diphenylketene)manganese *(3b)*.

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The composition of the monomeric, diamagnetic products *(3a)* and *(3b)* was established by elemental analysis and



spectroscopy; the yellow crystalline complexes are air-stable and decompose in a sealed tube on heating to 90 and 93 C respectively.

Table 1. Spectroscopic data of complexes *(1a)*, *(3a)*, and *(3b)*.

	IR [a] ν(M)—C≡O [cm⁻¹]		ν(C)=C=O [cm⁻¹]	^{1}H-NMR [b] τ(C_5H_4R)	τ(C_6H_5)	τ(CH_3)
				(ppm relative to internal TMS; in [D_6]-acetone)		
(1a) [3]	2026 vs (A_1)	1935 vs (E)		^{1}5.04 (5)		
(3a)	1999 vs (A_1)	1946 vs (B_1)	1787 m, br	^{1}5.45 (5)	≈ ^{m}2.8 (5)	
(3b)	1996 vs (A_1)	1943 vs (B_1)	1750 m, br	^{1}5.68 (4)	≈ ^{m}2.7 (5)	^{1}8.07 (3)

[a] ν(M)—C≡O frequencies in *n*-hexane, ν(C)=C=O frequencies in KBr.
[b] Intensities in parentheses; multiplicities given as superscripts preceding the τ values.

The IR spectra display two bands of almost equal intensity in the stretching region of metal-bonded carbonyl groups (Table 1). The loss of cumulative conjugation in the ketene system as a result of π conjugation with the central metal atom gives rise to a long-wave shift of the ν_{as}(C=)C=O band which appears at 2093 cm^{-1} (*n*-hexane) in the free

diphenylketene.—The mass spectra of *(3a)* and *(3b)* (70 eV; direct inlet: 75 and 85 °C respectively) indicate the occurrence of two synchronous fragmentation processes: apart from the loss of the diphenylketene ligand from the molecular ion, successive elimination of a total of three CO groups is also observed; one of these groups originates from the complexed diphenylketene, presumably with formation of a diphenylcarbene-metal fragment.—In addition to a sharp singlet for the η-cyclopentadienyl ligand, the 60-MHz ^{1}H-NMR spectrum of *(3a)* contains a somewhat broader signal for the phenyl protons. The significant upfield shift of the C_5H_5 signal in *(3a)* as compared to *(1a)* would suggest a transfer of charge density according to ketene→metal[3] and make a bonding of the ketene to the Mn atom *via* the carbonyl function appear rather unlikely owing to the high electronegativity of the O atom.

Formulation of the new compounds as π-olefin complexes also receives support from their chemical properties: whereas the cycloaddition of cyclopentadiene to free diphenylketene in boiling hexane is complete within 2 h[4], *(3a)* and *(3b)* react only very slowly under these conditions. However, the ketene ligand can be removed by reaction with triphenylphosphane in hexane at 60 °C (10 h) yielding $(C_5H_4R)Mn(CO)_2[P(C_6H_5)_3]$[5]. Reaction of *(3a)* with ethylene under pressure (55 atm, 80 °C, 12 h) in benzene leads to displacement of diphenylketene by ethylene, affording a 21% yield of dicarbonyl(cyclopentadienyl)(ethylene)manganese[6].

Procedure:

Diphenylketene[8] (10 mmol, 1.8 ml) is added at room temperature to a stirred solution of $C_5H_5Mn(CO)_2THF$ *(2a)* or $CH_3—C_5H_4Mn(CO)_2THF$ *(2b)*[7] (10 mmol), prepared by UV irradiation, in THF (50 ml) in an N_2 atmosphere. After 2 h the solvent is removed in a water-pump vacuum, and the deep red oily residue is taken up in benzene (5 ml) and chromatographed over alumina (Woelm, Activity I; water-cooled column). Compounds *(1a)* and *(1b)* and unreacted ketene are eluted with benzene, and *(3a)* and *(3b)* as pale-yellow zones with diethyl ether. After removal of solvent, recrystallization of the residue from *n*-hexane/diethyl ether (5:2) at −35 °C affords *(3a)* (2.1 g, 58%) or *(3b)* (2.0 g, 53%) as yellow crystals.

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[1] *O. S. Mills* and *A. D. Redhouse*, Chem. Commun. 1966, 444; J. Chem. Soc. *A 1968*, 1282.

[2] *P. Hong, K. Sonogashira*, and *N. Hagihara*, Tetrahedron Lett. *1971*, 1105; *D. A. Young*, Inorg. Chem. *12*, 482 (1973).

[3] *M. Herberhold* and *Ch. Jablonski*, Chem. Ber. *102*, 778 (1969).

[4] *H. Staudinger*, Liebigs Ann. Chem. *356*, 94 (1907).

[5] *R. S. Nyholm, S. S. Sandhu*, and *M. H. B. Stiddard*, J. Chem. Soc. *A 1963*, 5916.

[6] *H. P. Kögler* and *E. O. Fischer*, Z. Naturforschung *15b*, 676 (1960).

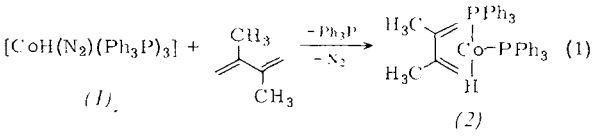
[7] *M. Herberhold*, Dissertation, Universität München 1963.

[8] *H. Staudinger*, Ber. Deut. Chem. Ges. *44*, 1619 (1911); *L. A. Feiler*, Dissertation, Universität München 1967.

2,3-Dimethyl-1,3-butadienehydridobis(triphenylphosphane)cobalt(I)

By *Peter Veit Rinze*[*]

Hydridocobalt(I) complexes $[CoHL_4]$ react with 1,3-dienes to form compounds of type $[Co(1—3\text{-}\eta\text{-allyl})L_3]$[1–3]. As in the isomerizations of coordinated allyl ligands[4], complexes $[CoH(1—4\text{-}\eta\text{-diene})L_n]$ may be expected to play an intermediate role in these reactions. They have long been postulated as active species in the oligomerizations of dienes catalyzed by cobalt complexes[5], but have hitherto been neither isolated nor detected by spectroscopy. This proves possible, however, on reaction of the dinitrogenhydridocobalt(I) complex *(1)* with 2,3-dimethyl-1,3-butadiene according to eq. (1).

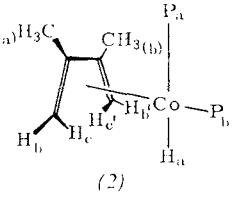


(1)

(1)

(2)

The yellow crystalline product *(2)* is extremely sensitive to air, turns deep red in N_2 above 40 °C, and decomposes above 70 °C. The IR spectrum of *(2)* in Nujol displays a Co—H stretching band at 1862 cm^{-1}. From the ^{1}H-NMR spectrum it may be deduced that at −50 °C in [D$_8$]toluene compound *(2)* exists almost exclusively as (1—4-η-2,3-dimethyl-1,3-butadiene)hydridobis(triphenylphosphane)cobalt(I), for which a trigonal-bipyramidal structure is proposed.



(2)

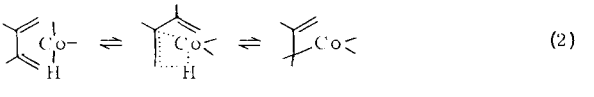
Table 1. ^{1}H-NMR data of the complex *(2)* at −50 °C in [D$_8$]toluene [a].

τ	Rel. int.	Coupling constants [Hz] [b]	Assignment
7.48	2		H_b
7.59			$H_{b'}$
8.08	3	$J(P_bCH_{3(a)})=3$	$CH_{3(a)}$
8.20	3		$CH_{3(b)}$
11.22	2	$J(P_bH_c)=12$	H_c
11.39		$J(P_bH_{c'})=15$	$H_{c'}$
27.7	1	$J(P_aH_a)=88$, $J(P_bH_a)=28$	H_a

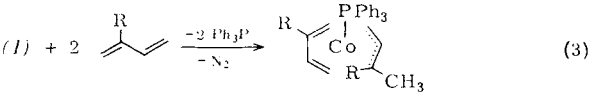
[a] 100 MHz; without phenyl proton signals. The solvent signal at τ = 7.90 was used as internal standard.
[b] All signals are relatively broad due in part to weak unresolved coupling effects.

The ^{1}H-NMR spectrum proves to be temperature dependent: the intensities of the resonance signals of H_a, $H_{b'}$, and $H_{c'}$ decrease with rising temperature; at −10 °C they have disappeared completely. The τ values of the other signals change by +0.13 ppm at most (for H_b). At 40 °C a new very broad signal appears at τ = 15.6 having a relative intensity of 3. Partial irreversible decomposition of *(2)* sets in at this temperature.

This dynamic behavior of *(2)* in solution can be described by eq. (2). However, no rearrangement occurs to give the



(2)



(3)

R = H[2], CH_3[6]

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(1—3-η-allyl) complex which is isolated as a stable product of the reaction according to eq. (3).

That this difference in reaction course is to be attributed not only to electronic effects of the additional methyl substituent but also to steric hindrance of the pentacoordination of the possible (1—3-η-allyl) compound is apparent from the existence of the corresponding (1—3-η-allyl) complexes $[Co(C_6H_{11})(CO)_3]$[1] and $[Co(C_6H_{11})(PF_3)_3]$[3].

Procedure:

All operations are carried out with solvents containing no H_2O or O_2 and under an inert gas. $[CoH_3(Ph_3P)_3]\cdot O(C_2H_5)_2$[7] (15.2 g, 16.5 mmol) in benzene (200 ml) is converted into *(1)* by treatment with N_2. After addition of C_6H_{10} (5.5 ml, 48.7 mmol) stirring is continued at about 20°C until evolution of gas has ceased. The brown solution is then concentrated in a vacuum and hexane is added (50 ml). Yellow crystals precipitate with simultaneous crystallization of benzene at 0°C. After drying at 10^{-1} torr *(2)* still contains benzene of crystallization (exp.: 77.35% C, 6.22% H; calc. for $C_{48}H_{47}CoP_2$: 77.40% C, 6.36% H). Yield 5.2 g (42%).

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German version: Angew. Chem. *86*, 351 (1974)

[1] *J. A. Bertrand, H. B. Jonassen*, and *D. W. Moore*, Inorg. Chem. *2*, 601 (1963).

[2] *P. V. Rinze* and *H. Nöth*, J. Organometal. Chem. *30*, 115 (1971).

[3] *Th. Kruck, G. Sylvester*, and *I.-P. Kunau*, Z. Naturforsch. *28b*, 28 (1973).

[4] *M. A. Cairns, J. F. Nixon*, and *B. Wilkins*, J. C. S. Chem. Commun. *1973*, 86.

[5] *P. Heimbach* and *R. Traunmüller*: Chemie der Metall-Olefin-Komplexe. Verlag Chemie, Weinheim 1970; and literature cited therein.

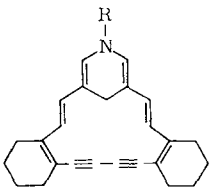
[6] *P. V. Rinze*, unpublished.

[7] *J. Lorberth, H. Nöth*, and *P. V. Rinze*, J. Organometal. Chem. *16*, P 1 (1969).

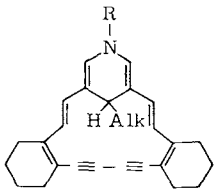
The Synthesis of Bridged "Didehydrooxa-" and "-thia[17]annulenes", Diatropic Homologs of Furan and Thiophene[1][***]

By *Julian M. Brown* and *Franz Sondheimer*[*]

The synthesis of the methylene-bridged "didehydroaza[17]-annulenes"[***] *(1)* to *(5)* has been described previously[1,2]. These are diatropic 18π-electron systems in which the magnitude of the ring current [*(1)* > *(2)* > *(3)* > *(4)* > *(5)*] was found to decrease with increasing electronegativity of the *N*-substituent. The derivatives *(6)* to *(8)* bearing alkyl groups within the cavity of the π-electron cloud have also been prepared[1,3]. The route used to obtain these aza[17]annulene derivatives has now been applied to the synthesis of the diatropic oxygen *(17)* and sulfur analogs *(18)* and *(19)* which were required so that we could study the effect on the ring current of varying the heteroatom within the same framework of a hetero-annulene. (For the preparation of paratropic and atropic *S*-oxides of *(18)* and *(19)* see ref.[4].)

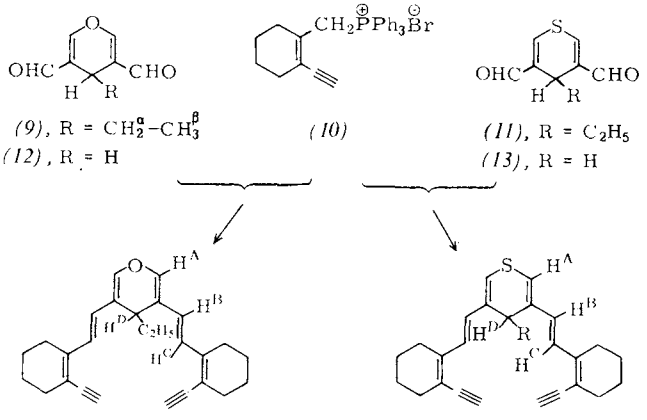


(1), R = ⊖
(2), R = CH_3
(3), R = H
(4), R = $COOC_2H_5$
(5), R = $COCH_3$



(6), R = ⊖
(7), R = CH_3
(8), R = H

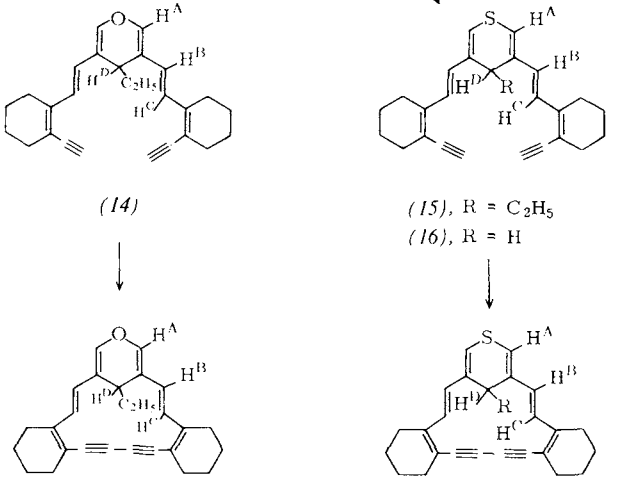
Wittig reaction of 4-ethyl-4*H*-pyran-3,5-dicarbaldehyde *(9)*[5] and 2 molar equivalents of the phosphonium salt *(10)*[6] in dimethylformamide with ethanolic lithium ethoxide at 90 C led to *ca.* 10% of the *trans,trans* isomer *(14)* as a pale yellow oil[7]. Oxidative coupling of *(14)* with cupric acetate in pyridine at 55—60°C under fairly dilute conditions gave *(17)*, a bridged "didehydrooxa[17]annulene", in 4% over-all yield [based on *(9)*]. Compound *(17)* forms yellow crystals, m.p. 167—168°C (decomp.); λ_{max} (cyclohexane) 260 sh (ε 8700), 305 sh (45000), 312 (47000), 365 (6100), 386 (6900), and 405 nm (6100).



(9), R = $CH_2^{\alpha}-CH_3^{\beta}$
(12), R = H

(10)

(11), R = C_2H_5
(13), R = H



(14)

(15), R = C_2H_5
(16), R = H

(17)

(18), R = C_2H_5
(19), R = H

The thiopyran *(11)*, m.p. 98—99 C, was prepared in 20% yield by hydrolysis of *(9)* with sodium carbonate and sodium hydroxide[8] in aqueous ethanol, followed by treatment with phosphorus pentasulfide in boiling toluene. Wittig reaction of *(11)* with *(10)*, and subsequent coupling of the resulting *(15)* (20% yield, yellow oil), as previously, then gave *(18)* in 13% over-all yield [based on *(11)*]. The bridged "didehydrothia[17]annulene" *(18)* forms orange-yellow crystals, m.p. 212—214°C (decomp.); λ_{max} ($CHCl_3$) 268 (ε 14500), 331 (54000), 361 (20800), 398 sh (9400), and 420 sh nm (6700).

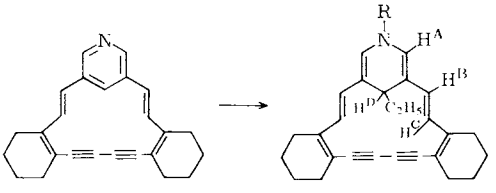
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[**] The award (to J. M. B.) of a Traveling Scholarship by the Australian National University is gratefully acknowledged.

[***] For the trivial "dehydroannulene" nomenclature used, see *F. Sondheimer* and *R. Wolovsky*, J. Amer. Chem. Soc. *84*, 260 (1962). We would like to continue to name diacetylenic annulenes "didehydroannulenes" or "bisdehydroannulenes" rather than "tetradehydroannulenes", in order to avoid confusion in the literature.

The starting material for the synthesis of the bridge-unsubstituted thia[17]annulene *(19)* was the thiopyran *(13)*, m. p. 169 °C, which was prepared in poor yield (1–6%) by ozonolysis of norbornadiene in acetone at −45 °C (dimethyl sulfide work-up), followed by treatment with phosphorus pentasulfide in boiling toluene[9]. Wittig reaction of *(13)* with *(10)*, as before, led to 45% of *(16)* as pale yellow crystals[10], oxidative coupling of which gave *(19)* (85% yield) as yellow crystals[10]; λ_{max} ($CHCl_3$) 265 sh (ε 13500), 333 (57000), 365 (26000), and 403 nm (9900).

For comparison with *(17)* and *(18)*, the bridge-ethyl aza[17]annulenes *(21)* to *(24)* were required. *(21)*[3] and *(22)*[11] have already been reported; *(23)*[10] and *(24)*[10] have now been prepared from the pyridine derivative *(20)*[2] in *ca.* 50% yield by reaction in tetrahydrofuran with ethyllithium (1 M in benzene) at −20 °C, followed by direct treatment with ethyl chloroformate and acetyl chloride, respectively[11].

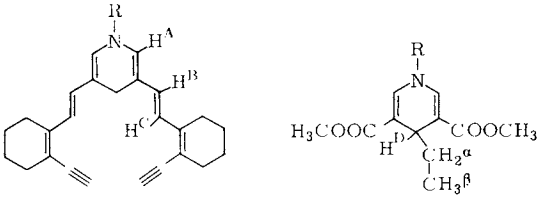


(20)

(21), R = CH_3
(22), R = H
(23), R = $COOC_2H_5$
(24), R = $COCH_3$

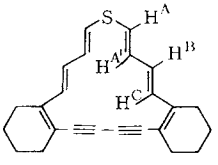
The ^{1}H-NMR chemical shift data of the bridge-ethyl hetero[17]annulenes *(17)*, *(18)*, and *(21)* to *(24)* are given in Table 1. The numbers in parentheses are the changes on passing from an appropriate atropic model to the heteroannulene. The models for *(17)* and *(18)* are the "open" precursors *(14)* and *(15)*, respectively. It was found impossible to prepare the "open" analogs corresponding to the aza[17]annulenes *(21)* to *(24)*; models chosen for these are the compounds *(25)* to *(28)*[2] containing no ethyl substituent (for H^A, H^B, H^C, and the allylic protons) and the diesters *(29)* to *(32)*[12] (for H^D, H^α, and H^β). It is evident from Table 1 that all the hetero[17]annulenes are diatropic, the outer proton resonances having moved to lower field as compared to the models, and the inner ones to higher field. The relative magnitude of these changes in both directions clearly shows the diamagnetic ring current to decrease in the order $NCH_3 > NH > S > O > NCOOC_2H_5 > NCOCH_3$.

The ^{1}H-NMR chemical shift data of the bridge-unsubstituted thia[17]annulene *(19)* are also given in Table 1, as well as the differences from the model *(16)* (parentheses). Comparison with the corresponding differences of the aza[17]annulenes *(2)* to *(5)*[2] shows that in this series the diamagnetic ring current also decreases in the order $NH > S > NCOOC_2H_5$. The ring current in *(19)* appears to be slightly greater than in the bridge-ethyl thia[17]annulene *(18)*. This effect of the ethyl group has already been found in the corresponding *N*-methylaza[17]annulenes[3], and is probably due to the greater deviation from planarity caused by this group.



(25), R = CH_3
(26), R = H
(27), R = $COOC_2H_5$
(28), R = $COCH_3$

(29), R = CH_3
(30), R = H
(31), R = $COOC_2H_5$
(32), R = $COCH_3$



(33)

The oxa[17]annulene *(17)* appears to be the first diatropic homolog of furan to be prepared[13]. The only previously described diatropic homolog of thiophene is the unbridged thia[17]annulene *(33)*[14]. In the ^{1}H-NMR spectrum of *(33)*, the chemical shifts of H^B (τ = 3.19), H^C (τ = 4.99), and the allylic protons (τ = 7.3—7.6)[15] are similar to those of *(18)* and *(19)* (Table 1). The bridge in *(18)* and *(19)* therefore does not appear to be particularly important for sustaining a diamagnetic ring current in these compounds.

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German version: Angew. Chem. 86, 346 (1974)

[1] Unsaturated macrocyclic compounds, Part 107.—Part 106: *P. J. Beeby, J. M. Brown, P. J. Garratt*, and *F. Sondheimer*, Tetrahedron Lett. *1974*, 599.

[2] *P. J. Beeby* and *F. Sondheimer*, J. Amer. Chem. Soc. *94*, 2128 (1972).

[3] *P. J. Beeby* and *F. Sondheimer*, Angew. Chem. *84*, 896 (1972); Angew. Chem. internat. Edit. *11*, 833 (1972).

[4] *J. M. Brown* and *F. Sondheimer*, Angew. Chem. *86*, 348 (1974); Angew. Chem. internat. Edit. *13*, 339 (1974).

Table 1. ^{1}H-NMR chemical shift data (τ values, 100 MHz, $CDCl_3$) of *(17)* to *(19)*, and *(21)* to *(24)* [a, b].

Compound	Outer H			Inner H			
	H^A	H^B	Allylic H	H^C	H^D	H^γ	H^β
(21) (NCH_3)	2.86 (−1.08)	2.47 (−1.13)	6.9 7.4 (−0.5)	6.55 (+3.30)	9.41 (+3.26)	10.14 (+1.56)	10.14 (+0.90)
(22) (NH) [c]	2.69 (−1.07)	2.54 (−1.03)	6.9 7.4 (−0.5)	6.39 (+3.13)	9.17 (+3.06)	10.08 (+1.55)	10.08 (+0.86)
(18) (S)	2.94 (−0.75)	2.90 (−0.72)	7.2 7.6 (−0.3)	4.72 (+1.99)	7.66 (+1.69)	9.36 (+1.00)	9.67 (+0.56)
(17) (O)	2.68 (−0.60)	3.19 (−0.62)	7.2 7.7 (−0.2)	4.27 (+1.43)	[d]	9.20 [e]	9.65 (+0.39)
(23) ($NCOOC_2H_5$)	2.43 (−0.58)	3.07 (−0.53)	7.2 7.7 (−0.2)	4.28 (+1.22)	[d]	9.23 (+0.82)	9.68 (+0.40)
(24) ($NCOCH_3$)	2.19 [f]	3.15 (−0.45)	7.2 7.7 (−0.2)	4.04 (+1.07)	7.28 (+1.16)	9.14 (+0.73)	9.64 (+0.34)
(19) (S)	3.10 (−0.76)	2.85 (−0.75)	7.2 7.6 (−0.3)	5.22 (+2.25)	8.98 (+2.26)		

[a] In addition, all compounds showed a band at τ ≈ 8.0—8.5 (aliphatic H).
[b] The assignments of H^B and H^C are based on nuclear Overhauser experiments and long-range coupling.
[c] Determined at −30 °C, due to line broadening at room temperature.
[d] The signal was obscured by the allylic H band.
[e] The signal in the model *(14)* was obscured by the aliphatic H band.
[f] The signal in the model *(28)* could not be located due to extreme broadening.

[5] This substance was prepared from malonaldehyde and propionaldehyde essentially according to *E. Winterfeldt*, Chem. Ber. 97, 1959 (1964).

[6] *P. J. Beeby* and *F. Sondheimer*, Angew. Chem. *85*, 406 (1973); Angew. Chem. internat. Edit. *12*, 411 (1973).

[7] All compounds, except *(12)* and *(29)* to *(32)*, were isolated by chromatography on alumina (Woelm, activity III). ^{1}H-NMR, UV, IR, and mass spectra compatible with the assigned structures were obtained for all new substances.

[8] See *F. Wille* and *L. Saffer*, Liebigs Ann. Chem. *568*, 34 (1950).

[9] The pyran *(12)*, m. p. 184—185 C, was similarly prepared by ozonolysis of norbornadiene, followed by treatment of the ozonide solution with zinc in acetic acid. However, the yield of *(12)* was very poor and irreproducible, and its further transformation to the oxygen analog of *(19)* could not be carried out.

[10] The substance decomposed on attempted melting point determination.

[11] The conversion of *(20)* into *(23)* was carried out by Dr. *P. J. Beeby*.

[12] The diester *(30)* (m. p. 108—109 C) was prepared from dimethyl pyridine-3,5-dicarboxylate [2] by reaction with ethylmagnesium bromide [3]. Treatment of *(30)* with sodium hydride, followed by addition of methyl iodide, ethyl chloroformate, or acetyl chloride gave *(29)* [3], *(31)* (m. p. 101—102 C), or *(32)* (m. p. 117 C), respectively.

[13] The previously prepared oxa[9]annulene (oxonin) [see *S. Masamune* and *N. Darby*, Accounts Chem. Res. 5, 272 (1972); *A. G. Anastassiou*, *ibid.* 5, 281 (1972)] and oxa[17]annulene [*G. Schröder*, *G. Plinke*, and *J. F. M. Oth*, Angew. Chem. *84*, 472 (1972); Angew. Chem. internat. Edit. *11*, 424 (1972)] appear to be atropic. For the synthesis of a paratropic oxa[15]annulene derivative, see *H. Ogawa*, *M. Kubo*, and *H. Saikachi*, Tetrahedron Lett. *1971*, 4859.

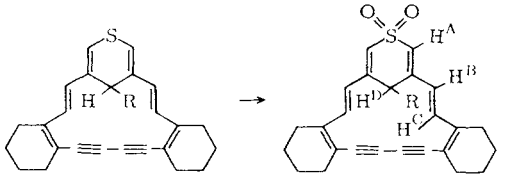
[14] *R. H. McGirk* and *F. Sondheimer*, Angew. Chem. *84*, 897 (1972); Angew. Chem. internat. Edit. *11*, 834 (1972).

[15] The chemical shift of H^A in the ^{1}H-NMR spectrum of *(33)* cannot be compared with those of *(18)* and *(19)*, since the double bonds adjacent to the sulfur atom in *(33)* appear to rotate (*P. J. Beeby*, *R. L. Wife*, and *F. Sondheimer*, unpublished experiments).

The Synthesis of Bridged "Didehydrothia[17]annulene" *S*-Oxides. The Dependence of Ring Current on Geometry in Stereoisomeric Sulfoxides[1]

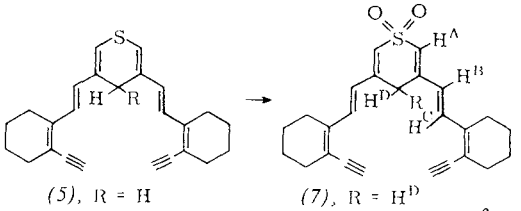
By *Julian M. Brown* and *Franz Sondheimer*[*]

The bridged "didehydrothia[17]annulenes" *(1)* and *(2)*[1] are shown by their ^{1}H-NMR to be diatropic, the sulfur atom presumably contributing two π-electrons to form



(1), R = H
(2), R = C_2H_5

(3), R = H^D
(4), R = CH_2^{α}–CH_3^{β}

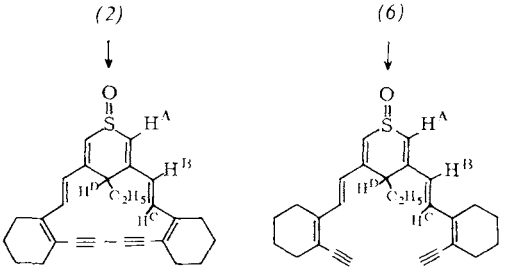


(5), R = H
(6), R = C_2H_5

(7), R = H^D
(8), R = CH_2^{α}–CH_3^{β}

an 18π-electron system. It was of interest to synthesize the corresponding *S*-oxides, in order to study their spectral properties. We now describe an investigation of the sulfones *(3)* and *(4)*, as well as of the stereoisomeric sulfoxides *(9)* and *(10)*.

Oxidation of the thia[17]annulene *(1)* with 2 molar equivalents of *m*-chloroperbenzoic acid in methylene chloride (−20 °C, 1 h) gave 65% of the sulfone *(3)*[2] as orange crystals[3] [λ_{max} ($CHCl_3$) 276 sh (ε 32000), 298 (53000), 310 (64000), 417 (4100), 437 sh (3100), and 467 sh nm (2800)]. Similar oxidation of the thia[17]annulene *(2)* (20 C, 2 h) led to 70% of the sulfone *(4)*[4] as yellow crystals [λ_{max}($CHCl_3$) 277 sh (ε 31000), 300 (67000), 313 (85000), 430 (2700), 444 sh (2600), and 479 sh nm (1500)]. Oxidation of the sulfides *(5)*[1] (−20 C, 2 min) and *(6)*[1] (20 C, 5 min) with 2 molar equivalents of the peracid gave the model" sulfones *(7)* and *(8)*[5] as pale yellow crystals in *ca.* 10% and 25% yield, respectively.

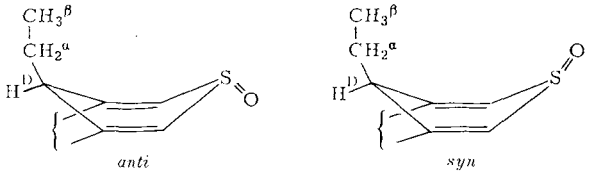


(2) *(6)*

(9), *anti*
(10), *syn*

(11), *anti*
(12), *syn*

Oxidation of the thia[17]annulene *(2)* with only 1 molar equivalent of *m*-chloroperbenzoic acid in methylene chloride (−20 C, 2 h) led to two stereoisomeric sulfoxides. The *anti*-isomer *(9)*, eluted first[2], was obtained in 25% yield as yellow crystals [λ_{max} ($CHCl_3$) 274 sh (ε 23000), 286 (35000), 311 sh (39000), 321 (43000), 412 (2800), 428 (2800), and 456 sh nm (1700)]. The *syn*-isomer *(10)*, eluted subsequently, was isolated also in 25% yield as orange crystals [λ_{max} ($CHCl_3$) 302 (ε 66000), 314 (75000), and 437 nm (1700)]. In order to obtain suitable models, the sulfide *(6)* was oxidized with 1 molar equivalent of the peracid (−20 C, 16 h); this reaction gave 15% each of the *anti*-sulfoxide *(11)* (eluted first) and the *syn*-sulfoxide *(12)* as cream-colored crystals. Attempts to oxidize the sulfides *(1)* and *(5)* containing no ethyl group to the corresponding sulfoxides were unsuccessful.



anti *syn*

The *anti* and *syn* structures (see diagrams) were assigned to the sulfoxides *(9)* and *(11)*, and *(10)* and *(12)*, respectively, on the basis of ^{1}H-NMR experiments using Eu(fod)$_3$ [tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III)]. Addition of this reagent caused the H^D signals to move downfield more quickly than either H^A or H^B in the *anti*-sulfoxides *(9)* and *(11)*, whereas the reverse was true in the *syn*-sulfoxides *(10)* and *(12)*.

The ^{1}H-NMR chemical shift data of the sulfones *(3)* and *(4)* and of the sulfoxides *(9)* and *(10)* are given in Table 1. The numbers in parentheses are the changes on passing from the "open" sulfones *(7)* and *(8)* and sulfoxides *(11)*

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and *(12)* to the corresponding macrocyclic compounds. The sulfones *(3)* and *(4)* are clearly paratropic, the outer proton signals having moved to higher field as compared to the models, and the inner ones to lower field. This is a reversal of the behavior of the sulfides *(1)* and *(2)*[1].

The stereoisomeric sulfoxides *(9)* and *(10)* show remarkably different ^{1}H-NMR spectra. The spectrum of the *syn*-isomer *(10)*, and the changes in chemical shift as compared to its model, are very similar to those of the sulfone *(4)*. The paramagnetic ring current in the *syn*-sulfoxide *(10)* is evidently similar in magnitude to that of the sulfone *(4)*. On the other hand, the *anti*-sulfoxide *(9)* exhibits a spectrum quite different from those of *(4)* and *(10)*, and the changes in chemical shift as compared to its model *(11)* show *(9)* to be atropic[6]. Similarly, the electronic spectrum of the *syn*-sulfoxide *(10)* resembles that of the sulfone *(4)*, but is different from that of the *anti*-sulfoxide *(9)*.

Table 1. ^{1}H-NMR chemical shift data (τ values, 100 MHz, $CDCl_3$) of *(3)*, *(4)*, *(9)*, and *(10)* [a, b]. For details see text.

Compound	Outer H			Inner H			
	H^A	H^B	Allylic H	H^C	H^D	H^γ	H^β
(3)	3.70 (+0.22)	3.97 (+0.24)	7.6–8.0 (+0.1)	1.33 (−1.21)	5.63 (−0.90)	–	–
(4)	3.67 (+0.21)	4.05 (+0.23)	7.6–8.0 (+0.1)	1.07 (−1.46)	4.64 (−1.58)	7.64 (−0.41)	8.88 (−0.28)
(9)	3.17 (−0.20)	3.72 (+0.03)	7.5–7.9 (0.0)	2.18 (−0.43)	5.41 (−0.58)	8.44 [c]	9.27 (−0.05)
(10)	3.59 (+0.28)	4.00 (+0.27)	7.6–8.0 (+0.1)	1.01 (−1.56)	4.63 (−1.60)	7.60 (−0.44)	8.80 (−0.29)

[a] In addition, all compounds showed a band at *ca.* τ = 8.0—8.5 (aliphatic H).
[b] The assignments of H^B and H^C are based on nuclear Overhauser experiments and long-range coupling.
[c] The signal in the model *(11)* was obscured by the aliphatic H band.

The conformations of the thiapyran ring in the sulfoxides *(9)* and *(10)* are presumably those shown in the diagrams, other conformations being disfavored for steric reasons. It is possible that the sulfur orbitals play a part in the observed difference in properties between *(9)* and *(10)*. However, it is tempting to speculate that this difference is due to the fact that the axial sulfoxide oxygen in the *syn*-isomer *(10)* has a 2p orbital which is ideally disposed for overlap with the π-perimeter, giving a paratropic "Möbius" 18π-electron system[7]. The corresponding 2p orbital of the sulfoxide oxygen in the *anti*-isomers *(9)* is not so disposed, and the molecule is consequently atropic. The reason for the paratropic nature of the sulfones *(3)* and *(4)* would then be the same as that proposed for the *syn*-sulfoxide *(10)*.

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German version: Angew. Chem. 86, 348 (1974)

[1] Unsaturated macrocyclic compounds. Part 108.—Part 107: *J. M. Brown* and *F. Sondheimer*, Angew. Chem. *86*, 346 (1974); Angew. Chem. internat. Edit. *13*, 337 (1974).

[2] All compounds were isolated by chromatography on silica gel (Woelm, activity II), unless indicated otherwise. ^{1}H-NMR, UV, IR, and mass spectra compatible with the assigned structures were obtained for all new substances.

[3] All new compounds decomposed on attempted melting point determination.

[4] Substance *(4)* was isolated by chromatography on alumina (Woelm, activity III).

[5] Substance *(8)* was isolated by direct crystallization since chromatography on silica gel effected little purification, and alumina caused isomerization to the corresponding 2*H*-thiapyran derivative.

[6] The downfield shifts of the inner H^C and H^D resonances in *(9)* are presumably due to local anisotropic effects [see *H. A. Staab* and *R. Bader*, Chem. Ber. *103*, 1157 (1970); *P. J. Beeby* and *F. Sondheimer*, J. Amer. Chem. Soc. *94*, 2128 (1972)] and are not accompanied by upfield shifts of the outer proton signals.

[7] We thank Dr. *H. M. R. Hoffmann* for this suggestion.

Synthesis of Homophthalic Acids by Copper-Catalyzed Direct Arylation of β-Dicarbonyl Compounds with 2-Bromobenzoic Acids.

By *Alle Bruggink* and *Alexander McKillop*[*]

We wish to report a simple, high yield procedure for the synthesis of homophthalic acids *(2)*. The method involves only two steps, namely (i) copper-catalyzed direct arylation of a β-keto ester with a 2-bromobenzoic acid and (ii) hydrolysis of the resulting α-acylhomophthalic acid half-ester *(1)*, $R^2 = OC_2H_5$, with dilute aqueous sodium hydroxide solution.

Other β-dicarbonyl compounds can be converted into substituted benzoic acids *(1)* in the same manner.

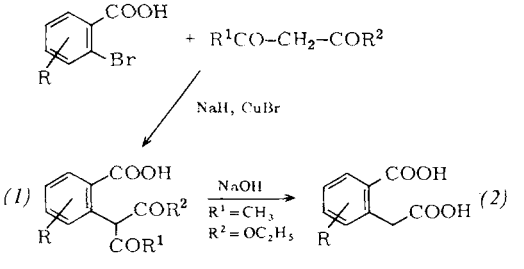


Table 1. Direct arylation of β-dicarbonyl compounds with 2-bromobenzoic acids to give compounds *(1)*, and hydrolysis of *(1)*, $R^2 = OC_2H_5$, to give homophthalic acids *(2)*.

R	R^1	R^2	Yield [%] *(1)*	Yield [%] *(2)* [a]
H	CH_3	CH_3	91	
H	CH_3	OC_2H_5	96	92
H	OC_2H_5	OC_2H_5	92	
H	C_6H_5	OC_2H_5	98	
4-CH_3	CH_3	CH_3	82	
4-CH_3	CH_3	OC_2H_5	99	88
4-CH_3	OC_2H_5	OC_2H_5	90	
4-NO_2	CH_3	CH_3	91	
4-NO_2	CH_3	OC_2H_5	98	90
4-NO_2	OC_2H_5	OC_2H_5	88	
5-CH_3O	CH_3	OC_2H_5	98	91
4,5-$(CH_3O)_2$	OC_2H_5	OC_2H_5	92	
3,4,5-$(CH_3O)_3$	CH_3	CH_3	84	
	OC_2H_5	OC_2H_5	84	

[a] Overall yield.

Treatment of 2-bromobenzoic acid with β-keto esters in the presence of sodium ethoxide and either copper powder or copper(II) salts gave erratic results which were difficult to reproduce[1–3]. The reaction mixtures obtained always con-

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sisted of at least three products: the desired compound *(1)*, unchanged 2-bromobenzoic acid, and 2-ethoxybenzoic acid, the latter compound in amounts up to 25%; separation of these mixtures was tedious and yields of pure *(1)* were low (15–45%).

We have found that direct arylation of β-keto esters and β-diketones can, however, be effected in excellent yield when a mixture of the reagents (using a 5—10 fold excess of the β-dicarbonyl compound) and sodium hydride is heated at 60—80 °C for 0.5—2 h in the presence of 6 mol-% of copper(I) bromide. Under these conditions competitive side reactions are eliminated and, consequently, isolation of the pure products *(1)* is straightforward (the reaction mixture is diluted with water, extracted with ether to remove the excess β-dicarbonyl compound, and the aqueous layer acidified with hydrochloric acid). Representative conversions are listed in Table 1.

Retro-Claisen condensation of the α-acylhomophthalic acid half-esters *(1)*, $R^2 = OC_2H_5$, is an extremely facile process owing to intramolecular catalysis by the carboxylate anion. Thus, when *(1)*, $R^1 = CH_3$, $R^2 = OC_2H_5$, is dissolved in aqueous 2 N sodium hydroxide solution at room temperature, both retro-Claisen cleavage of the acetyl group and hydrolysis of the ester function are complete within 20—30 minutes. The homophthalic acids *(2)* are obtained in virtually quantitative yield upon acidification (Table 1).

Received: February 4, 1974 [Z 998 IE]
German version: Angew. Chem. 86, 349 (1974)

[1] *W. R. H. Hurtley*, J. Chem. Soc. *1929*, 1870.

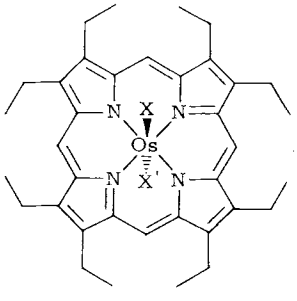
[2] *R. Adams* and *B. R. Baker*, J. Amer. Chem. Soc. *62*, 2208 (1940), and references therein.

[3] *D. E. Ames* and *W. D. Dodds*, J. C. S. Perkin I *1972*, 705.

Octaethylporphinatodioxoosmium(VI): An Extreme Metal Oxidation State within a Porphin System[**]

By *Johann Walter Buchler* and *Paul David Smith*[*]

Porphin derivatives of the homologs of iron, ruthenium[1] and osmium[2], have become known only recently. We now report the oxidation of carbonyl(octaethylporphinato)pyridineosmium(II) *(1)*[2] to octaethylporphinatodioxoosmium(VI) *(2)* with hydrogen peroxide[3].



The electronic spectrum [λ_{max} (log ε; CH_2Cl_2) = 578 (3.95), 470 (4.18), 428 (4.26), and 378 (5.09) nm] and the ^{1}H-NMR spectrum [δ($CDCl_3$) = 2.13 (t; CH_3), 4.25 (q; CH_2), and 10.75 (s; CH) ppm] show that the porphin ligand has remained intact. In the IR spectrum $\nu_{as}(OsO_2)$ appears at 825 cm^{-1} as the most prominent peak (*trans*-$[OsO_2Cl_4]^{2\ominus}$: 837 cm^{-1}[4]). Above 150 °C, *(2)* decomposes. Thus, no mass spectrum is available. Hitherto, hexavalent metals have not been found in metalloporphyrins[5, 6].

Cpd.	Os^n	X	X'
(1)	Os^{II}	CO	py
(2)	Os^{VI}	O	O
(3)	Os^{IV}	OCH_3	OCH_3
(4)	Os^{II}	py	py

Compound *(2)* is reduced by $SnCl_2$ in methanol to the orange Os^{IV} derivative *(3)*[3]. Finally, reduction of *(3)* with sodium dithionite in pyridine as well as photolytic decarbonylation of *(1)* in pyridine afford the Os^{II} derivative *(4)*[3].

The $Os^{II/IV/VI}$ system is the first porphin system in which the metal can take up or release a total of four electrons. This property is explained by the ability of the osmium atom to fit into the porphin ligand in all three oxidation states[6, 7].

Octaethylporphinatodioxoosmium(VI) (2)

Compound *(1)* (200 mg, 0.24 mmol) is dissolved in CH_2Cl_2 (15 ml) in a 50 ml wide-necked Erlenmeyer flask. Addition of CH_3OH (15 ml) is followed by dropwise addition of 30% H_2O_2 (2.5 ml). The mixture is allowed to stand for 1 h at 20 °C, and then heated to 60 °C for 3 h. After evaporation of the CH_2Cl_2, black needles of *(2)* (109 mg, ≈60%) are recovered by suction filtration and are washed with CH_3OH. Chromatography on neutral alumina (grade III) with CH_2Cl_2 yields a single olive-green zone of *(2)*. The compound is crystallized from CH_2Cl_2/CH_3OH and dried at 50 °C/10^{-3} torr.

Received: March 5, 1974 [Z 1 IE]
German version: Angew. Chem. 86, 378 (1974)

[1] *E. B. Fleischer*, *R. Thorp*, and *D. Venerable*, Chem. Commun. *1969*, 475; *G. W. Sovocool*, *F. R. Hopf*, and *D. G. Whitten*, J. Amer. Chem. Soc. *94*, 4350 (1972); *R. G. Little* and *J. A. Ibers*, J. Amer. Chem. Soc. *95*, 8583 (1973), and references cited therein.

[2] *J. W. Buchler* and *K. Rohbock*, J. Organometal. Chem. *65*, 223 (1974).

[3] C, H, N, and O analyses and determinations of molecular masses by osmometry in $CHCl_3$ gave correct values for *(2)*, *(3)*, and *(4)*. The electronic, IR, and mass spectra of *(3)* and *(4)* accord with the structural formulas given.

[4] *W. P. Griffith*, J. Chem. Soc. *A 1969*, 211.

[5] *E. B. Fleischer* and *T. S. Srivastava*, Inorg. Chim. Acta *5*, 151 (1971).

[6] *J. W. Buchler*, *L. Puppe*, *K. Rohbock*, and *H. H. Schneehage*, Chem. Ber. *106*, 2710 (1973).

[7] *R. D. Shannon* and *C. T. Prewitt*, Acta Crystallogr. *B 25*, 925 (1969); *B 26*, 1046 (1970).

[*] Prof. Dr. J. W. Buchler and P. D. Smith, M. S.
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[**] This work was supported by the Deutsche Forschungsgemeinschaft.

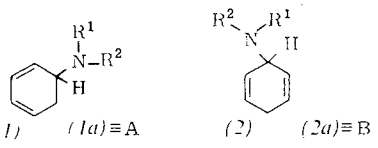
1,2-Photoaddition of Primary and Secondary Amines to Benzene

By *Derek Bryce-Smith*, *Andrew Gilbert*, and *Carl Manning*[*]

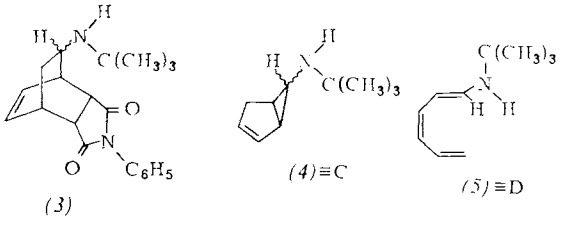
We have previously reported the 1,4-photoaddition of primary[1], secondary[1], and tertiary[2] amines to benzene, but we have now found that 1,2- and 1,3-adducts are also produced from primary, and 1,2-adducts from secondary, amines. Thus irradiation of an equimolecular mixture of *tert*-butylamine

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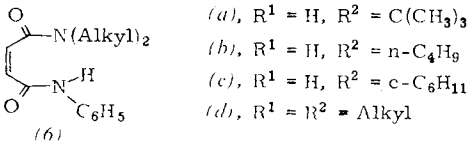
and benzene under nitrogen at 20 °C (low pressure Hg lamp) gave a basic pale yellow oil, b. p. 32 °C 0.02 torr[**] composed of four 1:1 adducts A, B, C, and D [GLC (Carbowax 20M), elution order C, D, A, B]. The proportions were time dependent.



(1) (1a) ≡ A (2) (2a) ≡ B



(3) (4) ≡ C (5) ≡ D



(6) (a), R^1 = H, R^2 = $C(CH_3)_3$; (b), R^1 = H, R^2 = n-C_4H_9; (c), R^1 = H, R^2 = c-C_6H_{11}; (d), R^1 = R^2 = Alkyl

Components A and B were primary products (*ca.* 1:1 ratio), and were shown (IR, NMR, MS) to be the 1,2-adduct *(1a)* and the 1,4-adduct *(2a)* respectively. Adduct *(1a)* gave the Diels-Alder adduct *(3)*, m. p. 195—198 °C, with *N*-phenylmaleimide, and was readily dehydrogenated (10% Pd on C) to give *N-tert*-butylaniline. Although B *(2a)* was stable under the irradiation conditions, the isolated component A *(1a)* readily photoisomerized to compounds C and D, giving a photostationary state where A:C:D ≈ 2:1:1, the first two components of which were separated by preparative GLC. Comparison of the spectral data for isomer C with those reported for bicyclo[3.1.0]hex-2-ene derivatives indicates the structure *(4)* (1,3-adduct)[***]. The adduct D was thermally and photochemically labile, yielding isomers *(1a)* and *(4)*, and could not be isolated in a pure state. The spectroscopic properties of the mixture enriched in D clearly indicated the 1,3,5-hexatriene structure *(5)*: rearrangements of compounds of this type to 1,3-cyclohexadienes and bicyclo[3.1.0]hexenes are well known.

Analogous reactions have been observed between *n*-butyl- and cyclohexyl-amine and benzene: the products were of the type described above, with minor variations in proportions. Benzene and secondary amines gave slightly different results. The proportion of 1,2-adduct *(1d)* was dependent upon the amine used, but in all cases examined (dimethyl-, diethyl-, di-*n*-butyl-amine, and piperidine) this was between 10 and 15%, the remainder being the 1,4-adduct *(2d)*. The spectroscopic properties of the 1,2-adducts *(1a)* to *(1c)* and *(1d)* were closely similar, but surprisingly the adducts *(1d)* showed no tendency to isomerize either thermally or photochemically, and *N*-phenylmaleimide gave benzene and the diamide *(6)*, with no trace of the expected Diels-Alder adducts. Although secondary amines (diethylamine, piperidine) rapidly react thermally (20 °C) with *N*-phenylmaleimide to yield compounds of type *(6)*, the corresponding reaction with primary amines is anomalous in being much slower; tertiary amines do not react. Hence reaction of the adducts *(1d)* with this dienophile may in principle involve an induced initial decomposition to give the free secondary amine, but it is not clear why the adducts of types *(2a)* to *(2c)* do not give diamides analogous to *(6)*.

Bicyclo[3.1.0]hexenes analogous to compound *(4)* are known to be formed by irradiation of benzene in the presence of certain alcohols and acids, but these appear to arise by a different mechanism involving thermal acid-catalyzed addition to benzvalene[3].

The present reactions provide a simple one-step route to amines of types not readily available by other procedures.

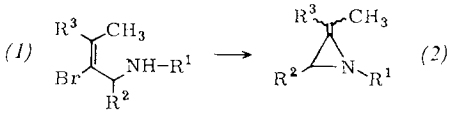
Received: February 26, 1974 [Z 999 IE]
German version: Angew. Chem. 86, 350 (1974)

[1] *M. Bellas, D. Bryce-Smith,* and *A. Gilbert*, Chem. Commun. *1967*, 862.
[2] *D. Bryce-Smith, M. T. Clarke, A. Gilbert, G. Klunklin,* and *C. Manning*, Chem. Commun. *1971*, 916.
[3] *L. Kaplan, D. J. Rausch,* and *K. E. Wilzbach*, J. Amer. Chem. Soc. *94*, 8638 (1972), and references therein.

2-Lithiated 1-*tert*-Butyl-3-methyleneaziridine and Its Reaction Products[**]

By *Helmut Quast* and *Carlos A. Weise Vélez*[*]

For a study of the stereochemistry of the thermal reorganization of methyleneaziridines[1] one requires suitably substituted derivatives. Although the preparation of 1-alkyl-2-alkylideneaziridines *(2)* (with or without substituents on C-3) by means of $NaNH_2$ in liquid NH_3 can be generalized, we attempted to modify *C*-unsubstituted methyleneaziridines *(5)*.



(1) (2)

(2a) [1], R^1 = Alkyl, R^2 = H, R^3 = CH_3
(2b) [2], R^1 = $C(CH_3)_3$, R^2 = CH_3, R^3 = H

Alkylation of 1-alkyl-2-methyleneaziridines *(5)* on the exocyclic methylene group in the presence of non-nucleophilic bases met with failure[1b], presumably because of the instability of the expected azirinium intermediates[3]. However, substitution of *(5b)* on the ring atom C-3 was accomplished, giving rise to the compounds *(7)*–*(9)*.

By experiments using ^3H-labeled NH_3 as solvent, *Bottini* and *Olsen*[4] had shown that *(5a)* is formed from *N*-propyl-2-bromoallylamine *via* the anions *(3a)* and *(4a)*[5]. Though no $^1H/^3H$ exchange occurs with $NaNH_2$ in liquid NH_3[4], we were able to generate 2-lithiated 1-*tert*-butyl-3-methyleneaziridine *(4b)*, M = Li, from *(5b)* by means of 1.5–2.0 mol of butyllithium/tetramethylethylenediamine (TMEDA) in ether at −78 °C. This product is colorless and stable up to *ca.* −50 °C.

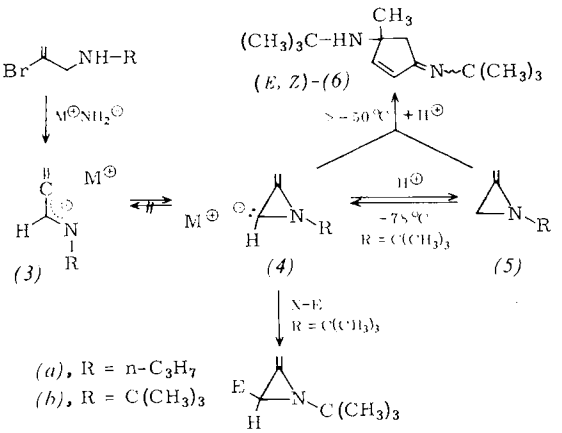
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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. The results are taken from the Diplomarbeit of *C. A. Weise Vélez*, Universität Würzburg 1974. We thank Mr. *V. Formáček*, Bruker-Physik AG, Karlsruhe, for the ^{13}C-NMR spectra. C. A. W. V. thanks the Deutsche Akademische Austauschdienst for a grant.

[**] Neutral components [2] were removed prior to distillation.

[***] The only slight inconsistency with published data [3] was that in the present case a *J* value of about 10 Hz was found for the olefinic protons whereas values of 5–6 Hz are reported for related examples.

When the solution of *(4b)*, M = Li, is treated with an electrophilic reagent (X—E) at −78 C to 0 C for 12 h, aqueous work-up and preparative GLC permitted isolation of the ring-substituted methyleneaziridines *(7)*—*(9)* as colorless liquids,



(7), E = D, (X-E = CH_3OD)
(8), E = CH_3, (X-E = CH_3J)
(9), E = $(CH_3)_3Si$, (X-E = $(CH_3)_3SiCl$)

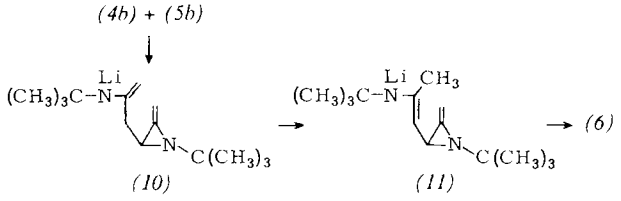
whose structures are proved by IR and ^{1}H-NMR spectra (all in CCl_4). *(7)* [+*ca.* 30% of *(5b)*], IR: 3100 (=CH_2), 2220 (—CHD—), 1770 cm^{-1} (C=C); ^{1}H-NMR (neat; 90 MHz); δ = 1.02 (s, 9H), 1.80 (mc, 1.3H), 4.37 (mc, 1H), 4.44 (mc, 1H). *(8)*, IR: 3090 (=CH_2), 1825 m, 1754 s, 1717 cm^{-1} m (C=C); ^{1}H-NMR (90 MHz): δ = 0.98 (s, 9H), 1.21 (dd, ^3J = 5.3 Hz, ^5J = 0.4 Hz), 4.30 (mc, 1H), 4.41 (mc, 1H). *(9)*, IR: 3095 (=CH_2), 1782, 1740 cm^{-1} (C=C); ^{1}H-NMR (60 MHz[6]): δ = 0.00 (s, 9H), 1.00 (s, 9H), 1.20 (mc, 1H), 4.33 (mc, 2H).

As expected, metalation of *(5b)* with *n*-butyllithium/TMEDA as described above proceeds more slowly than with *sec*-butyllithium/TMEDA. After 8 h at −70 to −60 C and addition of CH_3OD the product contained only 69% of *(7)* and 31% of *(5b)*[7]. Accordingly, use of methyl iodide furnished only 60—70% of *(8)* along with 30—40% of unchanged *(5b)*. However, with *sec*-butyllithium/TMEDA the anion *(4b)* is formed completely in 7.5 h at −78 C, as shown by its quantitative conversion into *(8)* or *(9)* by methyl iodide or trimethylchlorosilane, respectively.

Since methyleneaziridines *(5)* can be readily converted into α-chloroacetone[8], interesting possibilities result from using *(4)* and anions of other substituted methyleneaziridines as synthetic equivalents of enolates of α-hetero-substituted ketones.

A solution of *(4b)*, M = Li, becomes reddish-violet above −50 C and after 5.5 h at −78 to −15 C and addition of 1.5—2 mol of H_2O one obtains sublimable, pale yellow crystals, sensitive to air and moisture (m. p. 73—74 C, from pet. ether, yield 36%), which elemental analyses and mass spectrum show to be a dimer of *(5b)*. According to the ^{1}H-NMR spectrum in C_6D_6, two isomers are present in the ratio A : B = 3—4 : 1. The spectra prove the structure *(E,Z)-(6)*:

IR (Nujol): 3280 (NH), 3065, 3045 (=CH—), 1658 m, 1651 m, 1628 s, 1590 cm^{-1} w (C=N, C=C); ^{1}H-NMR (C_6D_6, 90 MHz) A: δ = 0.991 (s, NH—tBu), 1.08 (s, CH_3), 1.28 (s, =N—tBu), 2.36, 2.66 (AB, ^2J = 17.4 Hz, —CH_2—), 6.10, 6.31 ppm (AB, ^3J = 5.4 Hz, —HC=CH—). B[9]: δ = 0.986 (s, NH—tBu), 1.32 (s, =N—tBu), 2.56, 2.81 (AB, ^2J = 17.0 Hz, —CH_2—), 6.14, 6.49 (AB, ^3J = 5.8 Hz, —HC=CH—). In CD_3OD the AB quartet of the CH_2 group disappears owing to H/D exchange. ^{13}C-NMR of A (C_6D_6, 22.63 MHz): δ_c = 30.3 (q)[10], 31.8 (q), 32.5 (q), 46.4 (t), 51.6 (s), 55.6 (s), 65.4 (s), 135.6 (d), 154.1 (d), 170.7 ppm (s).



The formation of the dimer can be interpreted in terms of *(4b)* + *(5b)* → *(10)* → *(11)* → *(6)*. The step *(11)* → *(6)* is paralleled by the isomerization of vinylmethylenecyclopropanes[11] and their O-analogs[12].

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German version: Angew. Chem. 86, 380 (1974)

[1] a) *H. Quast* and *W. Risler*, Angew. Chem. 85, 411 (1973); Angew. Chem. internat. Edit. 12, 414 (1973); b) *W. Risler*, Diplomarbeit, Universität Würzburg 1973, and later experiments.

[2] *E*- and *Z*-form were separated by preparative GLC.

[3] *F. W. Fowler*, Advan. Heterocycl. Chem. 13, 44 (1971).

[4] *A. T. Bottini* and *R. E. Olsen*, J. Amer. Chem. Soc. 84, 195 (1962).

[5] This ring closure, which is only conrotatorily allowed and to which little attention has been paid hitherto, probably provides the first example of an electrocyclic reaction of an azaallyl anion.

[6] Using benzene as lock signal and secondary standard.

[7] Determined by mass spectrometry.

[8] *A. T. Bottini* and *J. D. Roberts*, J. Amer. Chem. Soc. 79, 1462 (1957).

[9] The signal of the CH_3 group of B and the NH signals are apparently obscured by other signals.

[10] The multiplicity of the corresponding signals in the off-resonance-decoupled spectrum is given in parentheses.

[11] *W. E. Billups*, *K. H. Leavell*, *E. S. Lewis*, and *S. Vanderpool*, J. Amer. Chem. Soc. 95, 8096 (1973), and references cited therein.

[12] *M. E. Hendrick*, J. Amer. Chem. Soc. 93, 6337 (1971); *A. C. Day*, *C. G. Scales*, *O. J. R. Hodder*, and *C. K. Prout*, J. C. S. Chem. Comm. 1970, 1228; *J. Grimaldi* and *M. Bertrand*, Bull. Soc. Chim. Fr. 1971, 957; *W. von E. Doering* and *L. Birladeanu*, Tetrahedron 29, 499 (1973).

A Pyridinium Ylide of 1,3-Indandione[**]

By *Hans Junek*, *Albin Hermetter*, and *Herwig Fischer-Colbrie*[*]

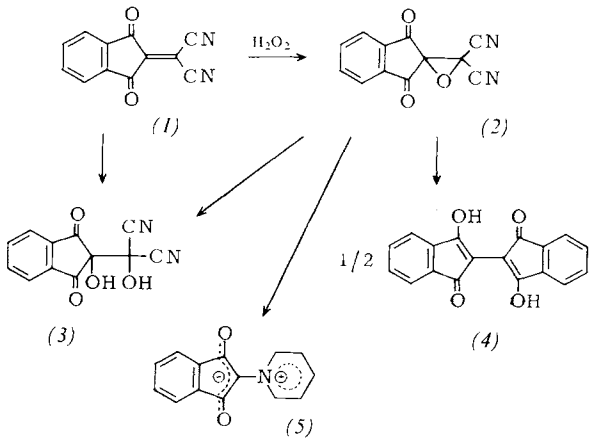
The exocyclic double bond in (1,3-dioxo-2-indanylidene)malononitrile *(1)* can be readily functionalized to give the epoxide *(2)* by heating with H_2O_2 (35%) in acetone. This reaction corresponds to the behavior of electron-deficient olefins on nucleophilic attack by hydrogen peroxide anions[1]. 1,3-Dioxospiro[indan-2,2'-oxirane]-3',3'-dicarbonitrile *(2)* is obtained in 50% yield [colorless needles, m. p. 205 C (from chlorobenzene)][2].

Compound *(2)* is relatively stable towards protic solvents: only after prolonged heating in glacial acetic acid is it converted into the dihydroxy compound *(3)* (40% yield). (2-Hydroxy-1,3-dioxo-2-indanyl)hydroxymalononitrile *(3)* is also obtained on treatment of *(1)* with H_2O_2 in glacial acetic acid [colorless needles, m. p. 280 C (dec.)][2].

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[**] Syntheses with Nitriles, Part 37. Part 36: *H. Junek*, *A. Hermetter*, and *H. Fischer-Colbrie*, Tetrahedron Lett. 1973, 2993.



Nucleophilic reactions proceed with great ease with the oxirane *(2)*; a mechanism involving formal elimination of mesoxalonitrile can be assumed. Thus on reaction of *(2)* with aniline, two indanyl groups combine to form 3,3'-dihydroxy-2,2'-bi-1-indenone *(4)*[3]. The reaction of *(2)* with pyridine in THF leads to a yellowish precipitate *(5)* within a few minutes. 3-Oxo-2-(1-pyridinio)-1-indenolate *(5)*, which can be formulated as an ylide, is a relatively stable compound and can be recrystallized from H_2O or acetonitrile [yellow needles, m.p. 255 °C, 60% yield, IR (KBr): 1580, 1610 cm^{-1}; MS: *m/e* (rel. int. %) = 167 (17), 223 (100); UV (C_2H_5OH): $\lambda = 390$ ($\varepsilon = 17700$), 310 (5350), 235 (30000), 220 nm (18500).

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[1] *A. Rieche* and *P. Dietrich*, Chem. Ber. 96, 1044 (1963); *W. J. Linn, O. W. Webster*, and *R. E. Benson*, J. Amer. Chem. Soc. 85, 1032 (1963).

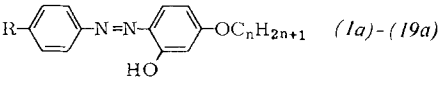
[2] The mass and IR spectra accord with the structures given. However, no nitrile band can be detected in *(2)* or *(3)*; see *H. Sterk* and *H. Junek*, Monatsh. Chem. 99, 810 (1968).

[3] *(4)* is identical with a reference sample prepared according to *H. Wittmann, A. Müller*, and *E. Ziegler*, Monatsh. Chem. *101*, 1389 (1970).

Low Melting Liquid Crystalline *o*-Hydroxy Azo- and Azoxybenzenes

By *Jan van der Veen* and *Theodorus C. J. M. Hegge*[*]

Recently a number of liquid crystalline salicylideneanilines were prepared[1]. As Schiff bases are unstable compared with azo- and azoxybenzenes it was thought worthwhile to investigate whether *o*-hydroxy substituted azo- and azoxybenzenes show liquid crystalline behavior too. The azo compounds were prepared by coupling of the appropriate diazonium tetrafluoroborate with resorcinol in acetone/water at a temperature between 0 and 5 °C. The *p*-hydroxyl group is alkylated by reaction of the potassium salt with an alkyl iodide in dimethylformamide to give the azobenzenes *(1a)*—*(19a)*[2] (Table 1).



(1a)-(19a)

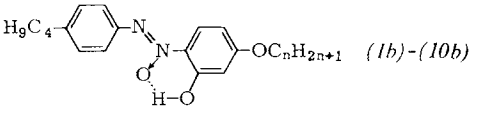
NMR and IR spectra[4] as well as elemental analyses were in accordance with the structures given above.

Compounds *(6a)* and *(7a)* are nematic at room temperature. *(6a)* showing a broad nematic range of 74 °C. Compounds *(1a)*—*(10a)* generally have clearing temperatures (T_c) similar to or somewhat higher than the corresponding compounds without an *o*-hydroxyl group[5]. This could be due to intramolecular hydrogen bonding leading to π-electron delocalization[6]. One can expect that the polarizability along the long axis of the molecules will be larger in *(1a)*—*(10a)* than in the unsubstituted analogs. Consequently the anisotropy in the polarizability and thus T_c[7] will be somewhat higher. No simple explanation can be offered for the minimum in the melting points within the homologous series *(1a)*—*(10a)*. Compounds *(1a)*—*(10a)* do not show the well-known *trans-cis* photoisomerization of azobenzenes since the *trans*-isomer is strongly stabilized by the intramolecular hydrogen bond. Compounds *(1a)*—*(10a)* were oxidized to *one* of the azoxy isomers *(1b)*—*(10b)*, as was indicated by NMR measurements (see experimental procedure and Table 2). The compounds gave correct elemental analyses.

Table 1. Melting points and clearing points (T_c) of the azobenzenes *(1a)*—*(19a)*.

Compound	*n*	M.p. [°C]	T_c [°C]
R = *n*-C_4H_9			
(1a)	1	68	60
(2a)	2	57	85
(3a)	3	54	62.5
(4a)	4	40	83
(5a)	5	36	74
(6a)	6	8 [a]	82
(7a)	7	23	79
(8a)	8	27	81.5
(9a)	9	36	80
(10a)	10	42	81
R = —CN [3]			
(11a)	1	188	167
(12a)	2	173	168
(13a)	3	160	144
(14a)	4	136	149
(15a)	5	104	140
(16a)	6	92	139
(17a)	7	89	133
(18a)	8	93	133 S → N 94 [b]
(19a)	9	85	128 S → N 116 [b]

[a] A second crystal modification has a m.p. of 17 °C.
[b] S = smectic, N = nematic.



(1b)-(10b)

Table 2. Melting points and clearing points (T_c) of the azoxybenzenes *(1b)*—*(10b)*.

Compound	*n*	M.p. [°C]	T_c [°C]
(1b)	1	82—84	80
(2b)	2	79	101.5
(3b)	3	68	82
(4b)	4	66	92.5
(5b)	5	59—61	88
(6b)	6	57	93
(7b)	7	53	91
(8b)	8	54	93
(9b)	9	63—65	91
(10b)	10	63	92

The clearing temperatures of *(1b)*—*(10b)* are very similar to those of the unsubstituted analogs[8].

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The static dielectric constants were measured at 1592 Hz for some typical compounds[9]. At 50 C compound *(6a)* has a dielectric anisotropy of 0.14 ($\varepsilon_{\parallel}=3.50$, $\varepsilon_{\perp}=3.36$). For the corresponding azoxybenzene [compound *(6b)*] at 60°C ($\varepsilon_{\parallel}=3.52$, $\varepsilon_{\perp}=3.69$) a dielectric anisotropy of −0.17 is found. Substitution of the butyl group in *(6a)* by a cyano group leads to a strong increase of the dielectric anisotropy as expected. For compound *(16a)* a dielectric anisotropy of 10.8 at 105 C is found ($\varepsilon_{\parallel}=16.9$, $\varepsilon_{\perp}=6.1$).

5-Ethoxy-2-(4-butylphenyl-NNO-azoxy)phenol (2b) from (2a)

Compound *(2a)* (2.0 g, 0.007 mol) is dissolved in acetonitrile (90 ml) and ethanol (20 ml). $NaHCO_3$ *(5g)* is added, followed by 30% hydrogen peroxide (20 ml). The reaction mixture is heated to its boiling point on a waterbath and allowed to cool down for 30 min at room temperature. After filtration to remove $NaHCO_3$ the filtrate is cooled to −20 C and then filtered once more. The precipitate [*(2b)*] is recrystallized from acetonitrile. Yield 1.2 g (57%) of *(2b)*.

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[1] *I. Teucher, C. M. Paleos,* and *M. M. Labes,* Mol. Cryst. Liq. Cryst. *11*, 187 (1970).

[2] *E. O. Woolfolk, E. Donaldson,* and *M. Payne,* J. Org. Chem. *27*, 2653 (1962).

[3] Thanks are due to Mr. *P. W. Janssen* for the preparation of these compounds.

[4] We are grateful to Mr. *H. M. van den Bogaert* and Mr. *C. H. van Hastenberg* for the recording and the interpretation of the IR and NMR spectra.

[5] *R. Steinsträsser* and *L. Pohl,* Z. Naturforsch. *26b*, 577 (1971).

[6] *V. I. Minkin, O. A. Osipov,* and *Yu. A. Zhdanov:* Dipole Moments in Organic Chemistry, Plenum Press, New York 1970, p. 258.

[7] *W. H. de Jeu* and *J. van der Veen,* Philips Res. Rep. *27*, 172 (1972).

[8] *R. Steinsträsser* and *L. Pohl,* Tetrahedron Lett. *1971*, 1921.

[9] *W. H. de Jeu* and *Th. W. Lathouwers,* unpublished results.

Rb_4P_6, a Phosphide with Planar Six-Membered Phosphorus Rings[1]

By *Walter Schmettow, Annegret Lipka,* and *Hans Georg von Schnering*[*]

On treating rubidium with red phosphorus (Solidex ampoule; Rb:P = 1:2.5; 450 C; 48 h; addition of a few milligrams of sulfur[2]) we obtained Rb_4P_6 as a compact black substance together with about the same amount of another, red, phosphide that has not yet been studied. Tetrarubidium hexaphosphide is instantaneously hydrolyzed in the air, yielding, along with monophosphane, first a pale yellow higher phosphane which within a few hours assumes a dark brown-to-black color.

In connection with the structure it is important that the compound is established as free from sulfur. Rb_4P_6 crystallizes orthorhombically in Fmmm with $a=9.641(1)$, $b=14.629(3)$ and $c=9.009(1)$ Å (Guinier-Simon photographs[3]); $Z=4$. The atoms occupy the following positions [x; y; z]: Rb(1) in 8g [0.2818; 0; 0], Rb(2) in 8f [1/4; 1/4; 1/4], P(1) in 8h [0; 0.1483; 0] and P(2) in 16m [0; 0.0734; 0.2053]. For 497 reflections $R=0.065$ and $R'=0.097$ (two-circle diffractometer data; Ag-Kα; solution by direct methods[4]).

The structure can be derived from the AlB_2 type by ordered removal of each fourth atom from the boron network. A

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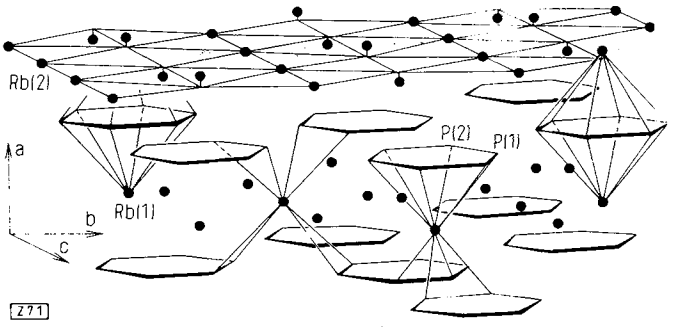


Fig. 1. Rb_4P_6 structure (Rb = black dots; P at the corners of the hexagons). The displacement of Rb(1) from the rubidium plane (above), and its relation to the hexagonal-bipyramidal Rb_2P_6 units, are indicated.

superstructure results in which structural units of AlB_2 type and NiAs type alternate along [011] and [01$\bar{1}$]. Isolated phosphorus six-membered rings thus appear in the Rb_4P_6 structure. These rings are exactly planar and regular to within experimental error (cf. Fig. 1). Each P atom is bivalent towards phosphorus and additionally surrounded trigonal-prismatically by six Rb atoms. The P—P separations in the six-membered ring amount to 2.149 (4×) and 2.150 Å (2×) with a standard deviation of ±0.008 Å, while the distances between the rings exceed 3.7 Å. Unlike the case of the AlB_2 structure, the Rb atoms do not lie strictly in one plane; Rb(1) is removed distinctly from the plane. Hexagonal-bipyramidal Rb_2P_6 units can be recognized, which are formed each from one P_6 ring and two Rb(1) and are connected by Rb atoms. Rb(1) is bonded to ten P atoms (3.46—3.55 Å), and Rb(2) to eight P atoms (3.56—3.62 Å).

It could be shown that the isotypic potassium compound K_4P_6 also exists [$a=9.361(1)$, $b=14.268(2)$, $c=8.644(1)$ Å][5]. A formal P_6^{4-} unit should contain four bivalent and two trivalent, but not six bivalent, P atoms. Rb_4P_6 and K_4P_6 are thus the first alkali-metal phosphides for which this simple, hitherto satisfactory, bonding concept[6] fails. Since the bonding rule needs to be obeyed only by semiconductors, these compounds could display metallic conductivity; otherwise double-bond contributions must be assumed in the P_6 ring; a bond order $n=1.16$ is in at least mathematical agreement with the short P—P separation of 2.15 Å.

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[1] Chemistry and Structural Chemistry of Phosphides and Polyphosphides, Part 10. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. Part 9: ref. [6].

[2] *W. Wichelhaus* and *H. G. von Schnering,* unpublished work.

[3] *A. Simon,* J. Appl. Crystallogr. *3*, 11 (1970).

[4] *P. Main, M. M. Woolfson,* and *G. Germain,* Program system GSR2, LSAM1, LSAM2; York (1969).

[5] *W. Hönle* and *H. G. von Schnering,* unpublished work.

[6] *H. G. von Schnering,* Nachr. Chem. Tech. *21*, 440 (1973).

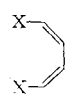
1,4-Dithiocin-6-yl Acetate

By *Henny J. Eggelte* and *Friedrich Bickelhaupt*[*]

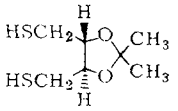
Particular interest attaches to the heterocyclic compounds *(1)*—*(3)* on account of a potential analogy with 10π electron systems[1,2]. Owing to the known analogy between a sulfur atom and a C=C group the aromatic character, if present at all, may be expected to be the most pronounced in 1,4-dithio-

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cin *(3)*. Hitherto, only extensively substituted derivatives of *(3)* were known which generally gave no indication of aromaticity[2].

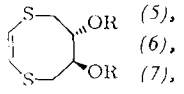


(1), X = O
(2), X = NH
(3), X = S

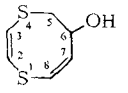


(-)-*(4)*

Our syntheses started from (−)-*(4)*[13], the dipotassium salt of which reacts with *cis*-1,2-dichloroethylene in boiling ethanol to give *(5)* (m.p. 54 C; yield 35%). Hydrolysis with 80% acetic acid at 75 C affords the diol *(6)* (m.p. 70 C; yield 85%) which reacts with mesyl chloride in pyridine to give the dimesylate *(7)* (m.p. 133 C; yield *ca.* 80%).



(5), R + R = $>C(CH_3)_2$
(6), R = H
(7), R = SO_2CH_3

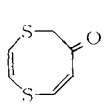


(8)

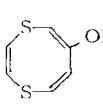
No 1,4-dithiocin *(3)* was obtained on reaction of *(5)* with various bases in various solvent systems. The major product was *(8)* [m.p. 45 °C; yield 5—25%; NMR ($CDCl_3$): δ = 6.25 (s, 2-H, 3-H), δ = 6.13 (m, 7-H, 8-H), δ = 5.05 (m, 6-H), AB part of an ABX system at δ = 3.88 and δ = 2.89 (5-H^a, 5-H^b), $J_{5a,5b}$ = 14 Hz, $J_{5a,6}$ = 5 Hz, and $J_{5b,6}$ = 7 Hz, δ = 2.56 ppm (br. s, OH)]. The yield of *(8)* was most reproducible and highest with KOH in DMF/water (3:1). *(8)* is optically active; the rotation of its acetate (m.p. 84 °C) in $CHCl_3$ amounts to $[\alpha]_D^{21} = 134°$.

Attempts to convert the alcohol *(8)* into *(3)* have so far been unsuccessful. In contrast, the preparation of *(10)* and *(11)* could be performed in the following manner: Oxidation of *(8)* with CrO_3 in HMPT for 16 h gave, in addition to 70% of unreacted *(8)*, the ketone *(9)* [yellow oil; yield 10%; NMR ($CDCl_3$): AB systems at δ = 7.10 and 6.21 (7-H, 8-H; J = 9 Hz), at δ = 6.77 and 6.68 (2-H, 3-H; J = 3 Hz), δ = 4.33 ppm (s, 2 5-H); IR ($CHCl_3$): 1665 cm^{-1}]. Treatment of *(9)* with lithium diisopropylamide in THF at −78 C followed immediately by reaction of the highly sensitive enolate with trimethylchlorosilane or acetyl chloride afforded *(10)* and *(11)*, respectively, in 30% yield.

Whereas *(10)* reverts to *(9)* on distillation or preparative thin-layer chromatography, 1,4-dithiocin-6-yl acetate *(11)* could be purified in this way and recrystallized from *n*-hexane/ether [m.p. 45 C; NMR (100 MHz, $CDCl_3$): AB systems at δ = 6.92 and 6.00 (7-H, 8-H; $J_{7,8}$ = 9 Hz with additional allyl coupling for 7-H: $J_{7,5}$ = 1 Hz), and 6.19 and 6.05 (2-H, 3-H; J = 9 Hz), δ = 5.76 (d, 5-H; $J_{7,5}$ = 1 Hz), δ = 2.17 (s, CH_3): UV (cyclohexane): λ_{max} = 225 (ε = 5380), 249 sh (3050), 255 sh (2550), 285 nm (3100); IR ($CHCl_3$): 1760 cm^{-1}; mass spectrum: *m/e* 43 (100%), 45, 94, 113, 158, 200 (M^+, 2%)[4].



(9)



(10), R = $Si(CH_3)_3$
(11), R = $COCH_3$

In accord with theoretical predictions[5], the spectroscopic properties do not appear to indicate an aromatic character of *(11)*, although the NMR spectrum (in particular) is not so clearly olefinic in character as that of *(1)*[2] so that the preparation of *(3)* is certainly still a matter of interest. Compound *(11)* does not form a Diels-Alder adduct with maleic anhydride, tetracyanoethylene, or hexafluoro-2-butyne. On heating above 50 C, *(11)* slowly decomposes with deposition of sulfur to give phenyl acetate, presumably *via* the *syn*-bisepisulfide[2].

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German version: Angew. Chem. 86, 381 (1974)

[1] *T. J. Katz*, J. Amer. Chem. Soc. 82, 3784, 3785 (1960).
[2] *E. Vogel, H.-J. Altenbach*, and *D. Cremer*, Angew. Chem. 84, 983 (1972); Angew. Chem. internat. Edit. 11, 935 (1972), and further references cited therein.
[3] *M. Carmack* and *C. J. Kelley*, J. Org. Chem. 33, 2171 (1968).
[4] As for *(5)*, *(6)*, *(7)*, *(8)*, and *(9)*, correct elemental analyses are also obtained for *(11)*.
[5] *B. A. Hess* and *L. J. Schaad*, J. Amer. Chem. Soc. 95, 3907 (1973).

Preparation and Properties of Tetraoxotechnetate(VI) and Tetraoxorhenate(VI)

By *Klaus Schwochau, Ludwig Astheimer, Jürgen Hauck*, and *Hans-Joachim Schenk*[*]

The existence of the oxoanions of hexavalent technetium and rhenium analogous to MnO_4^{2-} has not yet been established[1], although their formation has been postulated from spectrophotometric[2] and electrochemical[3] investigations.

We have now succeeded in preparing violet $[(CH_3)_4N]_2TcO_4$ and olive green $[(CH_3)_4N]_2ReO_4$ by controlled potential cathodic reduction of the tetramethylammonium salts of pertechnetate and perrhenate in acetonitrile with $(CH_3)_4NClO_4$ as supporting electrolyte. The pure crystalline compounds were deposited on a platinum electrode in a yield of more than 90%. The potential adjustment was based on the half-wave potentials measured polarographically for a one-electron transition ($E_{1/2}$ = −1.74 V for pertechnetate and $E_{1/2}$ = −2.30 V for perrhenate; saturated calomel electrode). Under similar conditions dark green $[(CH_3)_4N]_2MnO_4$ could also be precipitated; the half-wave potential of permanganate in acetonitrile was found to be $E_{1/2}$ = −0.60 V. Violet-blue K_2TcO_4 can be obtained by reduction of a solution of $KTcO_4$ in dimethyl sulfoxide at a mercury cathode. Tetraoxotechnetate(VI) and tetraoxorhenate(VI) are extremely sensitive to oxygen and atmospheric moisture which cause rapid oxidation and disproportionation; preparations must therefore be carried out in an inert atmosphere (argon) glovebox.

Susceptibility measurements on $[(CH_3)_4N]_2MO_4$ yielded magnetic moments of μ_{eff} = 1.61 (M = Mn), 1.56 (M = Tc), and 1.36 μ_B (M = Re), respectively. These values are in good agreement with theoretical predictions for tetrahedrally coordinated d^1-systems, where orbital contributions from excited states are not negligible. The compounds crystallize in isotypic cubic face-centered lattices with a = 11.09 (Mn), 11.20 (Tc), and 11.35 Å (Re); Z = 4. Reflection extinctions point to the space groups F23 or F$\bar{4}$3m; an unambiguous distinction presumes the localization of the hydrogen atoms. The metal atoms of the tetrahedral anions occupy the corners and the face centers of the unit cell, whereas the nitrogen atoms of the $(CH_3)_4N$ terahedra are placed at $\frac{1}{4}\frac{1}{4}\frac{1}{4}$. The structure resembles the antifluorite lattice.

Infrared measurements show the stretching modes of TcO_4^{2-} and ReO_4^{2-} to be shifted towards lower frequencies by almost 130 cm^{-1} compared to pertechnetate and perrhenate; the wave numbers are $\nu_3(F_2)$ = 780 and $\nu_4(F_2)$ = 340 cm^{-1} for TcO_4^{2-} and $\nu_3(F_2)$ = 785 and $\nu_4(F_2)$ = 325 cm^{-1} for ReO_4^{2-}.

Cubic splitting parameters of $\Delta_{tetr.}(TcO_4^{2-}) = -16.7$ kK and $\Delta_{tetr.}(ReO_4^{2-}) = -20.7$ kK were derived from diffuse reflectance spectra in the visible and ultraviolet. Both results compare

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favorably with the known value[4] $\Delta_{tetr.}(MnO_4^{2-}) = -12.0$ kK. The splitting of the $^2E(\Gamma_8) \rightarrow {}^2T_2(\Gamma_8)$ band indicates strong Jahn-Teller distortion of the oxoanions in the excited state.

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[1] *P. P. Pfeiffer*, Dissertation, Technische Hochschule Karlsruhe 1963; *B. Kanellakopulos*, Dissertation, Technische Hochschule Karlsruhe 1963.

[2] *C. L. Rulfs, R. A. Pacer*, and *R. F. Hirsch*, J. Inorg. Nucl. Chem. *29*, 681 (1967); *S. K. Majumdar, R. A. Pacer*, and *C. L. Rulfs*, *ibid. 31*, 33 (1969).

[3] *J. A. Shropshire*, J. Electroanal. Chem. Interfacial Electrochem. *16*, 275 (1968); *G. Kissel* and *S. W. Feldberg*, J. Phys. Chem. *73*, 3082 (1969); *S. J. Zhdanov, A. F. Kuzina*, and *V. I. Spitsyn*, Russ. J. Inorg. Chem. *15*, 803 (1970); *D. W. Letcher, T. J. Cardwell*, and *R. J. Magee*, J. Electroanal. Chem. Interfacial Electrochem. *30*, 93 (1971).

[4] *A. Carrington* and *M. C. R. Symons*, J. Chem. Soc. *1960*, 889; *P. Day, L. Disipio*, and *L. Oleari*, Chem. Phys. Lett. *5*, 533 (1970).

CONFERENCE REPORTS

2nd German-Danish Symposium on Organic Chemistry

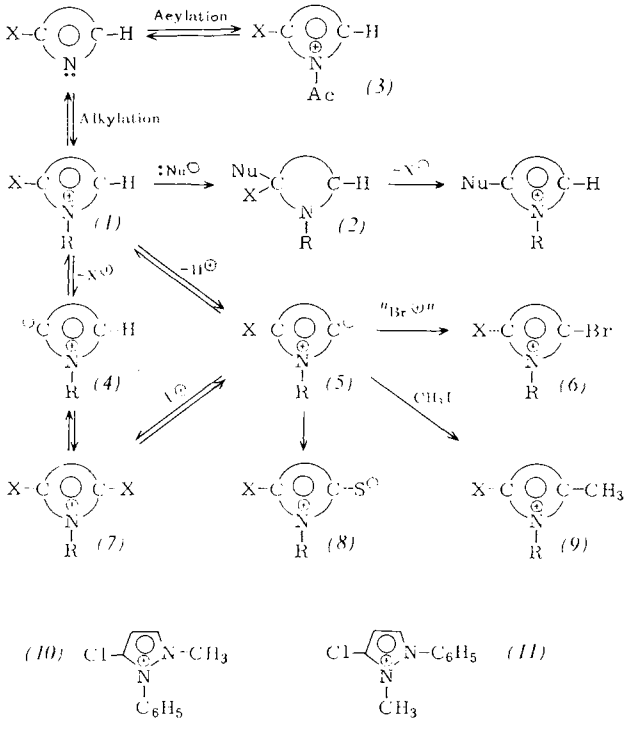
The Universities of Aarhus, Hamburg, Kiel, Copenhagen, and Odense organized a German-Danish Symposium on Organic Chemistry at Kiel from August 31 to September 2, 1973.

From the lectures:

Reactions of Azolium Salts with Nucleophilic Reagents

By *Mikael Begtrup*[*]

Azolium ions *(1)*[1] can react with nucleophilic reagents with substitution, proton abstraction, removal of a cation, dealkylation, or ring cleavage.



The substitution reactions of pyrazolium, imidazolium, and 1,2,3-triazolium salts are addition-elimination processes in which the addition step is rate-determining. The rate of substitution of azolium salts with different ring structures consequently increases with increasing stability of the intermediate *(2)*, which can be estimated from the resonance structures. This basis of assessment is inadequate for the prediction of the relative substitution rates of substitution isomers, *e.g. (10)* and *(11)*, since steric factors obviously become more important here. In this case one can determine the ratio of the substitution rates of a suitable pair of isomers. This empirical value normally depends only on the ring system and on the *N*-substituents.

The above-mentioned azolium salts react with electrophilic reagents in the presence of bases *via* the azolium ylides *(5)*. The formation of the ylide is rate-determining. The stability of the ylide can be estimated by measurement of the rate of the base-catalyzed replacement of the ring protons in the starting compound by deuterium.

The faster the deuterium exchange, the faster is the conversion into *(6)* *e.g.* with *N*-bromoacetamide and sodium methoxide. Stronger bases increase the rate of ylide formation. In the presence *e.g.* of sodium hydride in dimethylformamide, even substrates with weakly acidic ring protons react with sulfur and with methyl iodide to form *(8)* and *(9)*, respectively.

The rate of removal of cations, *e.g.* "$Br^{\oplus}$", from the azolium ions *(1)* increases with the stability of the resulting ylide *(4)* (which can again be determined from the rate of deuterium exchange).

In the case of azolium salts from which cations can be removed as well as protons, it is possible for the cation liberated to attack the ylide *(5)* formed by deprotonation, with formation of *(7)*.

This process is reversible, since *(7)* exists in equilibrium with the cations and the ylide *(4)*. The decisive steps for product formation are the nucleophilic substitution of *(1)* and *(7)*. This cation exchange explains the formation of anomalous substitution products of a series of azolium salts.

Acylazolium ions *(3)* can also lose cations. In these cases the free azole acts as the cation acceptor.

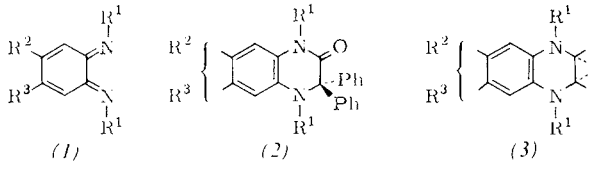
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[1] In "azolium salts" the cation consists of a five-membered ring with 6π electrons and at least two nitrogen atoms.

Cycloaddition Reactions of *o*-Quinonoid Compounds[**]

By *Willy Friedrichsen*[*]

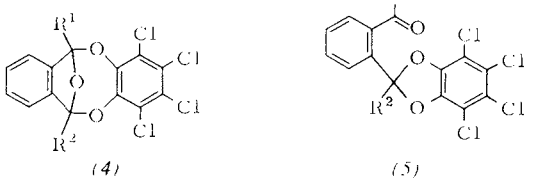
o-Benzoquinone diimides [*(1)*, R^1 = benzoyl, benzenesulfonyl; $R^2 = R^3 = H$; $R^2 = R^3 = CH_3$; $R^2 = H$, $R^3 = Cl$] react with diphenylketene and with olefins, like certain *o*-quinones[1], to form 2-oxo-1,2,3,4-tetrahydroquinoxalines *(2)* or 1,2,3,4-tetrahydroquinoxalines *(3)*[2]. Unsymmetrical *o*-benzoquinone diimides [*(1)*, R^1 = benzoyl, benzenesulfonyl; $R^2 = H$, $R^3 = Cl$] form both regioisomers *(2)* in the former case; the structures of the isomers were determined by partial synthesis.



(1) *(2)* *(3)*

Kinetic studies (activation parameters, solvent dependence of the rate constants, competition experiments) agree with the assumption that the reactions leading to *(2)* and *(3)* are Diels-Alder reactions with inverse electronic requirements.

1,3-Diarylisobenzofurans react with *o*-quinones thermally to form 6,11-epoxydibenzo[*b*,*f*][1,4]dioxocins *(4)* and/or dioxoles *(5)*[3] (formulated for the reaction with tetrachloro-*o*-benzoquinone). Investigations on the mechanism [reaction of 1-(tetramethylphenyl)-3-phenylisobenzofuran to form *(5a)* (R^1 = tetramethylphenyl, R^2 = phenyl)[4] and *(5b)*



(4) *(5)*

(R^1 = phenyl, R^2 = tetramethylphenyl), (activation parameters, by measurement of the temperature dependence of the rate constants and of the product distribution)] show that the reaction is entropy-controlled and proceeds *via* an isopolar transition state.

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[**] In collaboration with Dipl.-Chem. *H.-G. Oeser* and *Regine Schmidt*.

[1] Review: *G. Pfundt* and *G. O. Schenck* in *J. Hamer*: 1,4-Cycloaddition Reactions. Academic Press, New York 1967, Chap. 11.

[2] According to this, at least some of the results obtained by *R. Adams et al.* (review: *R. Adams* and *W. Reifschneider*, Bull. Soc. Chim. Fr. *1958*, 23) must be corrected.

[3] See also: *W. M. Horspool*, *J. M. Tedder*, and *Z. U. Din*, J. Chem. Soc. *C 1969*, 1964.

[4] *(5a)* was synthesized by an independent route.

Steric Effects in the Mass Spectra of Monocyclic and Bicyclic Diols and Their Derivatives

By *Hans-Friedrich Grützmacher*[*]

The differences in the mass spectra of stereoisomeric compounds are partly due to elimination reactions of the molecular ions, which must proceed *via* a transition state with a specific steric arrangement. Since the steric conditions for the transition state can be easily checked with the aid of molecular models, a mass-spectrometric identification of stereoisomers is possible in this way without the use of reference spectra.

It is known that a stereospecific 1,4-elimination of H_2O occurs in the molecular ions of cyclohexanol. Investigation of the mass spectra of stereoisomers of the cyclopentanediols, cyclohexanediols, and cycloheptanediols, and their dimethyl ethers also show stereochemical control for the elimination of HOR (R = H, CH_3) and CH_2O from the molecular ions if the substituents occupy the 1,3 or 1,4 positions. In the *trans* compounds the elimination of HOR dominates the fragmentation, whereas the elimination of CH_2O is characteristic of the *cis* compounds. The stereochemical control of the fragmentations also persists in *C*-methylated derivatives of 1,3-cyclohexanediol, with the exception of the 2-methyl and 2,2-dimethyl derivatives, in which fast ring cleavage of the molecular ions occurs.

Surprisingly, however, the expected steric effects cannot be detected in the mass spectra of the positional isomers and stereoisomers of the bicyclo[2.2.1]heptanediols and their dimethyl ethers. On the other hand, the expected effects are again observed in the mass spectra of decalindiols and of corresponding dimethyl ethers, so that mass-spectrometric identification of the stereoisomers is possible in this series of compounds. It is interesting to note that stereochemical control of the elimination reactions is also found for the 1,5-dimethoxydecalins if the methoxy groups can come close together in any conformation of the molecular ions.

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Constitution of the Polymers and the Coordination Compounds of Formaldehyde Oxime[**]

By *Kai Arne Jensen*[*]

Evidence obtained from chemical properties and infrared spectra shows that "triformoxime" or "trimeric formaldehyde oxime" is actually a chain polymer. The known acetyl and benzoyl derivatives of formaldehyde oxime are, however, derivatives of a cyclic trimer, 1,3,5-trihydroxyhexahydro-1,3,5-triazine. Similarly, the known hydrochloride, $(H_2CNOH)_3HCl$, and also other salts, contain the cyclic trimer, but on neutralization they depolymerize to formaldehyde oxime. The cyclic trimer could, however, be prepared by a special method. It is readily soluble in water but is rapidly transformed into the water-insoluble polymer. In aqueous solution it is partially depolymerized to formaldehyde oxime.

Analysis of the ^1H-NMR spectra of solutions of $(H_2CNOH)_3HCl$ in deuterium oxide has shown that, in aqueous solution, an equilibrium exists between monomeric and trimeric formaldehyde oxime and, at higher pH values, is shifted completely towards the monomeric form.

The hydrochloride, $(H_2CNOH)_3HCl$, forms very intensely colored coordination compounds with nickel, iron, and manganese salts. There has been some doubt whether these complexes are derived from monomeric or trimeric formaldehyde oxime. According to above mentioned studies the ligand must be the anion of monomeric formaldehyde oxime. This is substantiated by a detailed infrared spectroscopic investigation of the complexes, as well as by other physical methods. In

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[**] In collaboration with *Flemming A. Andersen*, *Arne Holm*, *Borge Nygaard*, and *Carl Th. Pedersen*.

the course of our studies the compounds were prepared in a pure state for the first time. The transition metal in the three complexes has the oxidation state 4+, also in the iron compound which has hitherto been formulated with iron(III).

Reaction between Electrophiles and Electrolytically Generated Anions

By *Henning Lund*[*]

Transfer of an electron to a neutral molecule produces a radical anion which may react as a radical, a nucleophile, or a base.

In the two latter cases a neutral radical is produced which may accept an electron, thus forming an anion capable of reacting with a proton or an electrophile. If the reaction of the electrophile with anion radicals or anions is to compete with their reaction with protons, the medium must be aprotic.

Electrophiles are generally reducible. In the present investigation we used substrates which are more easily reduced than the electrophiles; direct electron transfer to the latter is avoided by control of the electrode potential.

In dimethylformamide acetic anhydride may be used as electrophile in a reductive acetylation of nitro compounds to *N,O*-diacetylated hydroxylamines. Nitrogen- and other heterocyclic compounds may be reductively acetylated in a similar manner.

Alkyl halides or other alkylating agents may be used as electrophiles too. Fluorenone may be reductively methylated to 9-methoxy-9-methylfluorene with methyl chloride. Other types of compounds have been reductively alkylated, such as mono- and diketones, imines, and disulfides.

The mechanism of the reaction between the radical anion and an electrophile such as methyl chloride seems best descibed as an S_N2-like reaction rather than an electron transfer in solution to the alkyl halide followed by a reaction between an alkyl radical and a substrate radical anion.

The reactivity of a given radical anion depends on its counter ion. Large cations, such as tetrabutylammonium ions, form loose ion pairs, and the anion is thus relatively reactive; Li^+ may be regarded as an electrophile which reacts reversibly with the anion.

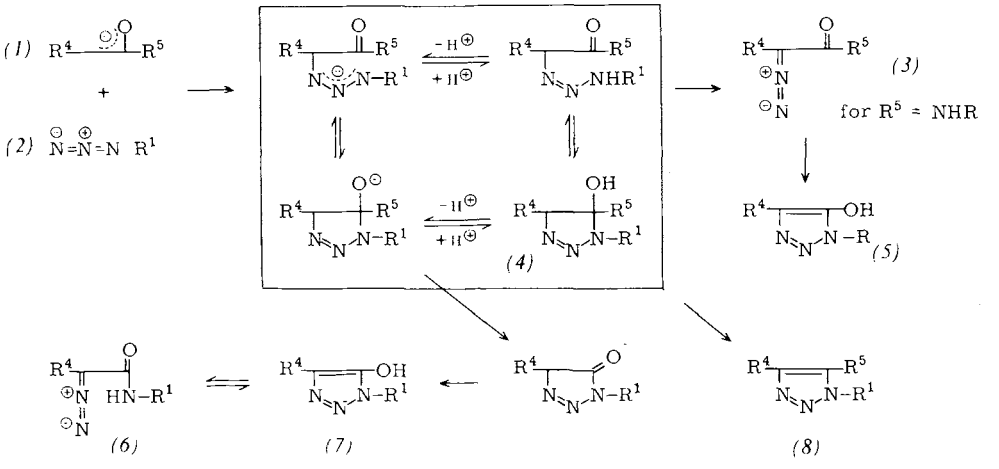
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1,2,3-Triazolines

By *Carl Erik Olsen*[*]

5-Hydroxy-Δ^2-1,2,3-triazolines *(4)* were early postulated as intermediates in the Dimroth reaction[1], but were not isolated. They also play an important part in the "diazo group transfer reaction"[2].

In the present work, a series of compounds *(4)* were prepared by reaction of monoketones *(1)* with organic azides *(2)* in the presence of potassium *tert*-butoxide. The investigation of their chemical properties led to the scheme shown[3] for the possible base-catalyzed reactions of carbonyl-activated methylene compounds with azides. Which of the possible end products are formed [*(3)* or *(5)*, *(8)*, or *(7)* or *(6)*] depends on the position of the equilibria shown inside the box, the leaving ability of the groups R^1NH and R^5, and the kinetic acidity of the 4-H atom.



On treatment with acid, the triazolines *(4)* yield 1,2,3-triazoles *(8)* or, after removal of nitrogen and 1,2-rearrangement, α-amino ketones or amides.

The stereochemistry at C-4 and C-5 was determined by NMR spectroscopy. The triazoline ring appears to assume an envelope conformation, with the hydroxyl group axial and R^1 equatorial.

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[1] *G. L'Abbe*, Ind. Chim. Belge *36*, 3 (1971).

[2] *M. Regitz*, Angew. Chem. *79*, 786 (1967); Angew. Chem. internat. Edit. *6*, 733 (1967).

[3] *C. E. Olsen*, Acta Chem. Scand., in press.

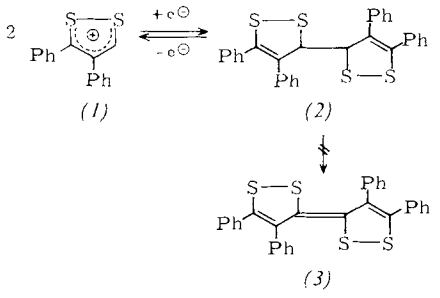
New Aspects of 1,2-Dithiole Chemistry

By *Carl Th. Pedersen*[*]

Cathodic reduction of 3,4-diphenyl-1,2-dithiolylium salts such as *(1)* in acetonitrile on a platinum electrode is accompanied by the formation of a dimer *(2)*[1]. The structure of the dimer was confirmed by the formation of 1,2,5,6-tetraphenylhexane upon Raney nickel desulfurization. Attempts to convert the

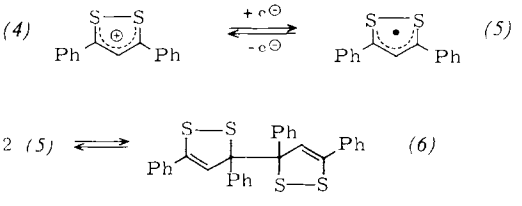
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dimer *(2)* into the tetrathiofulvalene *(3)* by electrochemical or chemical methods have been without success.



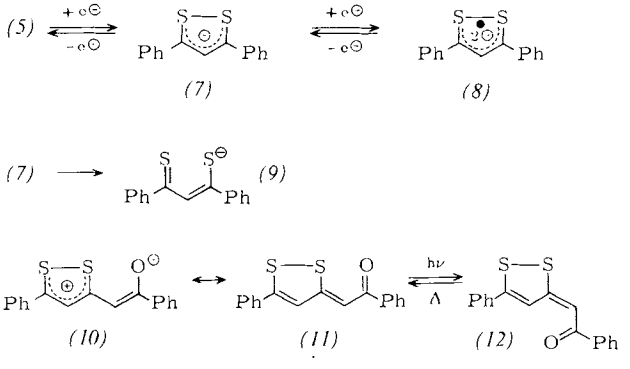
(1) *(2)* *(3)*

In contrast to the "irreversible electrochemistry" of *(1)* the electrochemistry of its 3,5-diphenyl analog *(4)* was completely reversible[2, 3]. Preparative reduction of the salt resulted in the formation of a grass-green solution which displayed a well resolved ESR spectrum. This was taken as evidence for the formation of the stable radical *(5)*. At lower temperature



(4) *(5)* *(6)*

the color faded and the ESR signal disappeared, at higher temperature the color and the ESR signal reappeared, possibly indicating an equilibrium between *(5)* and *(6)*. Further reduction resulted in the formation of the anion *(7)* and the dianion radical *(8)*. The anion *(7)* was not stable and was rapidly converted into the propanedithionate *(9)*.



(7) *(8)* *(9)* *(10)* *(11)* *(12)*

Photolysis of *(4)* in ethanol resulted in the formation of *(5)* and *(9)*[4]. Although dithiolylidene ketones *(11)* can be considered a kind of inner dithiolylium salts *(10)*, the photochemistry of *(11)* was quite different from that of dithiolylium salts. Irradiation of *(11)* in cyclohexane or ethanol resulted in the formation of the *trans* form *(12)* which reverted to the starting material by a dark process[5]. The rate constant for the thermal back reaction was found to be strongly dependent upon the steric requirements of the substituent in position 4 of the dithiole ring.

[1] *C. Th. Pedersen* and *V. D. Parker*, Tetrahedron Lett. *1972*, 767.

[2] *C. Th. Pedersen, K. Bechgaard*, and *V. D. Parker*, J. C. S. Chem. Comm. *1972*, 430.

[3] *K. Bechgaard, V. D. Parker*, and *C. Th. Pedersen*, J. Amer. Chem. Soc. *95*, 4373 (1973).

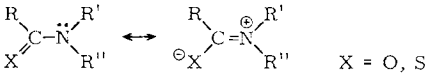
[4] *C. Th. Pedersen* and *C. Lohse*, Tetrahedron Lett. *1972*, 5213.

[5] *C. Th. Pedersen* and *C. Lohse*, J. C. S. Chem. Comm. *1973*, 123; J. C. S. Perkin I *1973*, 2837.

NMR Spectroscopic Studies on Hindered Rotation in Primary Amides and Thioamides

By *Ernst Schaumann*[*]

The (thio)amide system is planar as a result of resonance. The anisochronism of the substituents on the nitrogen that is to be expected on the basis of canonical formula *(2)* cannot generally be detected for primary (thio)amides (R′=R″=H), since the NH_2 signal is strongly broadened because of the quadrupole moment of the ^{14}N nucleus. The quadrupole broadening can be eliminated by irradiation at the ^{14}N resonance frequency, and a sharp AB quadruplet is recorded for the NH_2 protons[1]. According to the result of the benzene dilution method and the long-range coupling constants, which are resolved in the case of thioformamide (R=R′=R″=H, X=S), the *cis* proton (R″=H) in thioamides (X=S) is more strongly shielded than the *trans* proton (R′=H), whereas the opposite shielding pattern is found for amides (X=O) at room temperature. In ^{15}N-labeled compounds the $^1J_{^{15}N-^1H}$ coupling having the greater magnitude occurs with the *trans* proton in amides and with the *cis* proton in thioamides.



(1) *(2)* X = O, S

The free energies of activation $\Delta G^{\neq}$ determined from the coalescence of the NH_2 signals are about 3 kcal/mol higher for the primary thioamides, corresponding to a stronger contribution of the canonical formula *(2)*, than for the amides. Moreover, the $\Delta G^{\neq}$ values are distinctly dependent on the hydrogen bond acceptor capacity of the solvent, and for R=alkyl they decrease with increasing size of R and simultaneously increasing positive inductive effect. For R=aryl, a resonance interaction of the (thio)carbonyl group with the aromatic ring competes with the (thio)amide resonance; this interaction is strongest for R=*p*-anisyl (*p*-$CH_3OC_6H_5$) and leads to a rotation barrier that is 0.7 kcal/mol lower than for R=C_6H_5, X=S. A comparison of the $\Delta G^{\neq}$ values found for the primary (thio)amides with the known rotation barriers for *N,N*-dimethyl-(thio)amides (R′=R″=CH_3)[2] shows that for R=H and R=CH_3 the *N*-methyl substitution leads to intensified hindrance of rotation as a result of the positive inductive effect of the methyl group, whereas for R=$C(CH_3)_3$, the steric effect of the substituents on the nitrogen is decisive, and particularly low barriers are found for the tertiary compounds.

On addition of trifluoromethanesulfonic acid, a new signal appears in the spectrum of thiobenzamide at $\delta = 6.37$ ppm (in $CDCl_3$); this signal is not affected by ^{14}N decoupling, but is split with $^3J_{^{15}N-^1H} = 2$ Hz in the case of the ^{15}N compound, and must therefore be regarded as the signal of an SH proton[3]. The increased hindrance of rotation that is to be expected on *S*-protonation is also observed (in $CH_3NO_2/C_6D_5NO_2$, $\Delta G^{\neq} = 17.9$ kcal/mol; on addition of acid, $\Delta G^{\neq} > 19.4$ kcal/mol).

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[1] *W. Walter, E. Schaumann*, and *H. Rose*, Tetrahedron *28*, 3233 (1972); Org. Magn. Res. *5*, 191 (1973).

[2] *W. Walter, E. Schaumann*, and *J. Voss*, Org. Magn. Res. *3*, 733 (1971).

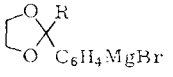
[3] *M. F. Sieveking*, Diplomarbeit, Universität Hamburg 1973.

The Electronic Effect of Phosphorus and Its Preparative Consequences

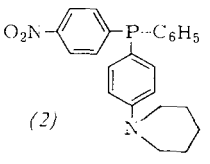
By *G. P. Schiemenz*[*]

The question of the electronic effect of phosphorus as a substituent on the benzene ring led to a need for aromatic phosphanes with (if possible several) second order substituents, and the answer opened up new synthetic pathways.

The sum of the electronic effects of the phosphane phosphorus results in electron acceptor qualities, so that an electrophilic aromatic substitution is possible only in exceptional cases, *e.g.* in the *m*-nitration of triphenylphosphane, in which the phosphorus is not oxidized under controlled conditions; under more severe conditions, the reaction yields (m-O_2N—$C_6H_4)_3PO$, from which tris(m-nitrophenyl)phosphane is obtainable on the 100 g scale by reduction with $HSiCl_3$. The phosphanes (o-, m-, p-CH_3CO—$C_6H_4)_n(C_6H_5)_{3-n}P$, $n=1,2,3$ (only $n=1$ for the *ortho* compound) and p-$(C_6H_5)_2P$—C_6H_4CHO can be prepared by side-chain oxidation and reduction with $HSiCl_3$; the triarylphosphanes containing an o-, m-, or p-acetyl or formyl group in one, two, or three aromatic rings are more readily obtainable from $(C_6H_5)_{3-n}PCl_n$, $n=1$, 2, 3, and the o-, m-, and p-dioxolanyl derivatives *(1)*, R = CH_3, H, with subsequent hydrolysis of the dioxolane ring[1].



(1)



(2)

The acceptor effect of the phosphorus is partly mesomeric, so that particularly in phosphane chalcogenides, o- and (more easily) p-halogen, above all fluorine, can undergo nucleophilic substitution, *e.g.* with R_2N, RHN, HO, NC, and O_2N groups. In $C_6H_5P(X)(C_6H_4$—F-$p)_2$, X = O, S, both fluorine atoms can be replaced by two identical or different groups; the products include (after reduction with $HSiCl_3$) $C_6H_5P(C_6H_4NO_2$-$p)_2$ and chiral phosphanes such as *(2)*, an ideal compound for the discussion of the possibilities of conjugation through phosphorus[2].

Hammett correlations of the phosphanes with acceptor substituents in the *para* position show for reaction on the phosphorus that the σ scale and not the σ^- scale is valid for the acceptors. This confirms the earlier result that even in these particularly favorable systems, the phosphane phosphorus is unable to exert any appreciable $+M$ effect. The evaluation method makes it possible for the first time to obtain information about the electronic effect of phosphorus from reactions on the phosphorus itself rather than on the second substituents[1].

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[1] Results of *H. Kaack*.

[2] Results of *M. Finzenhagen*.

A Convenient Method for the Conversion of Aldehydes into Nitriles[**]

By *Erich Vowinkel*[*]

Aldehydes can be converted into nitriles under very mild conditions and in quantitative yields by treating their oximes with dicyclohexylcarbodiimide (DCC) in the presence of copper(II) halides to form the corresponding isoureas, which decompose spontaneously with loss of *N,N'*-dicyclohexylurea. The entire process is carried out without isolation of the intermediates, and is complete in 1—3 hours at room temperature.

$$R{-}CHO + NH_2OH \xrightarrow[2)\ Cu^{2+},\ N(C_2H_5)_3]{1)\ \text{pyridine},\ H_2O,\ HCl} R{-}CN$$
$$\text{DCC},\ CH_2Cl_2$$

In pyridine/water the first step proceeds quantitatively. The second step, addition of the aldoxime to the carbodiimide, occurs selectively if the DCC is stabilized against the direct attack of water in the two-phase system by addition of triethylamine.

This method fails when oxime formation is disturbed. In the case of the aromatic o-hydroxy aldehydes, for example, the OH group must first be blocked. For this purpose we used benzyl ether protective groups, which can later be removed by hydrogenolysis without affecting the nitrile group (yields 95—99%).

The rate-determining step of the nitrile formation is the addition of the aldoxime to the carbodiimide. With a 20% excess of DCC this step follows first-order kinetics, since the intermediate complex that is assumed to be formed from Cu^{2+}, halide ions, and carbodiimide ligands has only a limited solubility. Electronic and steric factors have little or no influence on the rate of the nitrile formation. Some examples of preparative yields, based on the aldehydes, are: 99.5% for 3-nitrobenzonitrile; 99.4% for 4-diethylaminobenzonitrile; 97.1% for 3-methoxy-2,6-dinitrobenzonitrile; and 97% for ferrocenecarbonitrile.

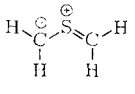
[*] Doz. Dr. E. Vowinkel
Institut für Organische Chemie der Universität
23 Kiel, Olshausenstrasse 40—60 (Germany)

[**] Studies by *J. Bartel*.

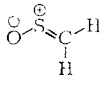
Perturbed Electrocyclic Reactions: A Three-Membered Ring Example

By *James P. Snyder*[*]

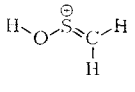
Simple thiocarbonyl *S*-oxides are known to decompose under a variety of conditions to give the corresponding ketone or aldehyde and sulfur. Cyclization to a three-membered ring can be considered to be a reasonable, but at present experimentally unverified, first step in the reaction. In order to gain an insight into the possible mechanism of the process, the electrocyclic closure of the sulfur series *(1)*—*(4)* has been investigated by an MO-CNDO-SCF procedure.



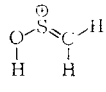
(1)



(2)



(3)



(4)

The thiocarbonyl derivative *(1)* behaves exactly as expected for a π-analog of the allyl anion. Conrotatory closure is allowed ($\Delta E = 15$ kcal/mol); disrotatory forbidden ($\Delta E > 37$ kcal/mol). Surprisingly both conrotatory *and* disrotatory closures of the protonated *S*-oxides *(3)* and *(4)* are predicted to be allowed from an orbital symmetry point of view and of similar energy ($\Delta E = 28$ and 29 kcal/mol respectively). This result arises from

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an energy reordering of both the π-HOMO of the open systems *(2)*—*(4)* and the in-plane lone pair sulfur orbitals for the corresponding three-membered rings relative to the symmetrical ylide *(1)*. The overall consequence of substitution of an electronegative group (*i.e.* $O^{\ominus}$, OH) for CH_2 is an orbital correlation which differs entirely in character from that of the allyl anion case. The energy equivalence of conrotatory and disrotatory closure for *(3)* and *(4)* suggests a variety of stereochemical consequences for similar systems perturbed strongly by substitution.

German version: Angew. Chem. 86, 313 (1974)
[VB 378 IE]

ABSTRACTS

Reviews

Abstracts of selected progress reports and review articles

Antiaromaticity is discussed in a review by *R. Breslow*. A cyclic conjugated system is considered to be antiaromatic if its π-electron energy is higher than that of the reference compound which is not cyclically delocalized. Suitable reference compounds are, *e.g.*: for cyclobutadiene *(1)* the open-chain analog 1,3-butadiene *(2)* (alternatively: two isolated



(1) *(2)* *(3)* *(4)*

ethylene molecules); for the cyclopropenyl anion *(3)* the allyl anion *(4)* (alternatively: a carbanion and a double bond in isolated molecules). Major antiaromatic effects have been detected in both these systems and in the cyclopentadienyl cation. In the case of higher membered systems it is difficult to decide whether or not they are antiaromatic in the sense of the energy definition. [Antiaromaticity. Accounts Chem. Res. *6*, 393—398 (1973); 38 references]

[Rd 692 IE—L]

Membrane-active polypeptides from snake venom—cardiotoxins and hemocytotoxins—are reviewed by *E. Condrea*. In addition to the snake-venom basic polypeptides exhibiting neurotoxic activity, a new group of basic polypeptides showing hemolytic, cytolytic, depolarizing, and cardiotoxic effects have recently been studied. These polypeptides exhibit pronounced structural similarities and a relatively low toxicity for animals. They can be grouped together as membrane-active polypeptides which modify cell membrane structures and impair membrane function, and thus prepare the way for the action of snake venom on normally inaccessible membrane substrates. For instance, they favor the action of phospholipase from snake venom while themselves exhibiting only slight lytic activity. Polypeptides and enzymes from snake venom act synergically. Different cell types react differently toward membrane-active polypeptides, *e.g.* neoplastic cells more readily than normal ones. The article also discusses changes in the membrane due to interaction of S—S groups of the polypeptides with SH groups of the membrane, linkage with membrane by way of electropositive charges, and penetration of the membrane structure with the aid of lipophilic side chains. [Membrane-active Polypeptides from Snake Venom: Cardiotoxins and Haemocytotoxins. Experientia *30*, 121—129 (1974); 58 references]

[Rd 696 IE—M]

The problems of MO calculations for inorganic systems with incompletely filled valence shells are discussed in a review by *P. G. Burton*. The various ways of introducing the simplifications and approximations necessary to render the specific problem economical for calculation are critically assessed. Possible directions for future improvements in the evaluation of wave functions useful for *prediction* of physical properties are indicated. [Current Methods in MO Theory for Inorganic Systems and Their Future Development—An Interpretative Review. Coord. Chem. Rev. *12*, 37—71 (1974); 75 references]

[Rd 698 IE—H]

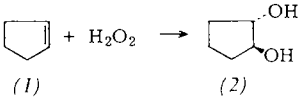
Present knowledge about binuclear oxo-bridged iron(III) complexes is reviewed by *K. S. Murray*. Methods of synthesis are outlined, X-ray diffraction data, optical, ESR, NMR contact shift, and Mössbauer spectra and magnetic susceptibilities are given and interpreted. The electronic structure of the Fe—O—Fe dimers is discussed mainly in terms of spin-spin coupling of $S = 5/2$ iron(III) units. An account of oxo-bridging in important biological iron systems is also included. [Binuclear Oxo-Bridged Iron(III) Complexes. Coord. Chem. Rev. *12*, 1—35 (1974); 141 references]

[Rd 699 IE—H]

Patents

Abstracts of selected "Deutsche Offenlegungsschriften" (DOS), *i.e.* provisionally published specifications as filed with the German Patent Office

Glutaraldehyde *(3)* is obtained in good yields together with *trans*-1,2-cyclopentanediol *(2)* by reaction of cyclopentene *(1)* with anhydrous hydrogen peroxide. Esters of phosphonic acid are suitable solvents, and suitable catalysts are *e.g.* soluble



(1) *(2)*

(1) + 2 H_2O_2 → OHC-$(CH_2)_3$-CHO + 2 H_2O

(3)

molybdenum compounds. The reaction can also be applied to other olefins. [DOS 2201456; Bayer AG, Leverkusen]

[PR 179 IE G]

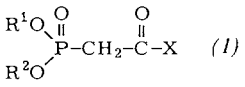
Diglycolic acid *(2)* is formed in yields of 80—93% by oxidation of diglycol *(1)* with oxides of nitrogen. The reaction is preferably carried out in 30—70% nitric acid at 40—90 °C.

$$\underset{(1)}{HOCH_2CH_2OCH_2CH_2OH} + 4NO_2 \rightarrow \underset{(2)}{HOOCCH_2OCH_2COOH} + 4NO + 2H_2O$$

[DOS 2206862; Badische Anilin- & Soda-Fabrik AG, Ludwigshafen]

[PR 180 IE G]

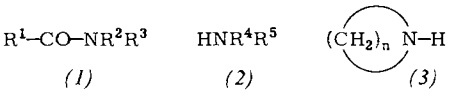
Phosphonoacetic acid and its salts and amides having the general formula *(1)* (X = NH_2 or OR^3; R^1, R^2, R^3 = H, NH_4, substituted ammonium, alkali metal, or alkaline earth metal), particularly phosphonoacetic acid itself and *e.g.* its monoammonium salt, have regulatory effects on plant growth. In low concentrations they act as growth inhibitors, and in higher concentrations as herbicides. [DOS 2318254; Merck & Co., Inc., Rahway, N. J. (USA)]



(1)

[PR 182 IE S]

Continuous production of organic isocyanates from primary amines or from their salts and phosgene utilizes amides of organic acids *(1)* or amines *(2)* or *(3)* as catalysts in a quantity of 0.1—10%; the reaction is carried out at 0 to 25 °C. [DOS 2121183; Magyar Tudomanyos Akademia, Budapest]

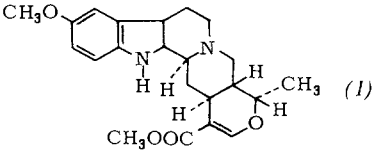


(1) *(2)* *(3)*

R^1 = H, dialkylamino, N-containing heterocycle
R^2 = H
R^3 = H, alkyl
$R^2 + R^3$ = alkylene
R^4, R^5 = alkyl, aralkyl, cycloalkyl
n = 1—7

[PR 151 IE—J]

Cubacine *(1)*, **a methoxyheteroyohimbine derivative having sympatholytic properties** with minimal side effects, can be obtained from *Cabucala cryptophlebia*, *C. plectanlifolia*, and *C. crassifolia*. [DOS 2147805; Forschag, Forschungs- und Chemie AG, Basel]



(1)

[PR 155 IE—K]

4-(2-Hydroxybutoxy)-2-butanol *(1)* can be used as a cholagogue because of its low toxicity and its high activity. The reaction of 1,2-butylene oxide with 1,3-butanediol in the presence of basic catalysts has proved particularly suitable for its preparation. [DOS 2164847; Nippon Zoki Pharmaceutical Co. Ltd., Osaka]

$$CH_3{-}CHOH{-}(CH_2)_2{-}O{-}CH_2{-}CHOH{-}C_2H_5 \quad (1)$$

[PR 156 IE—K]

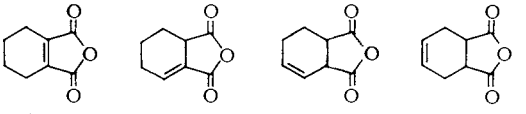
Carbon fibers having cation exchange properties are obtained by treatment of carbon fibers with a mixture of 2—96 wt.-% of nitric acid, 2—45 wt.-% of potassium dichromate, and 2—80 wt.-% of water at temperatures up to the boiling point of the solution. The treatment time is 5 min to 10 h. The procedure described leads to only a slight decrease in the mechanical strength of the fibers, which can be used at pH 3—12. The wettability of the fibers and their ability to be bonded when used for the production of fiber-reinforced plastics are improved. [DOS 2205122; Kureha Kagaku Kogyo K. K., Tokyo]

[PR 163 IE—A]

Heat-resistant thermoplastic polyesters are obtained by the use of 4,4'-bis(2-hydroxyethoxy)tetraphenylmethane as the diol component in the production of polyesters by conventional methods from aromatic and possibly aliphatic dicarboxylic acids and possibly other aliphatic or cycloaliphatic diols, particularly ethylene glycol, together with small quantities of cross-linking compounds. Polyesters obtained in this way have glass transition temperatures of up to 120 °C. Because of the higher glass transition temperatures, the range of application of the polyesters is significantly extended. In particular, they are suitable for the production of heat-resistant moldings for the electrical industry. [DOS 2218518; Sandoz AG, Basel]

[PR 165 IE—T]

By isomerization of 1,2,3,6-tetrahydrophthalic anhydride *(4)* on a rhodium catalyst, one can obtain *(1)*, *(2)*, and *(3)*, which are more suitable than *(4)* *e.g.* for the production of tetraazaporphin pigments. The products are essentially isomer mixtures that consist of various quantities of the individual isomers [*e.g.* more than 80 wt.-% of *(1)*] according to the reaction conditions (80—250 °C) or that are liquid at room temperature. The rhodium catalyst may also be used for the isomerization of derivatives of *(4)*, *e.g.* esters or low alkyl derivatives. *(4)* is readily obtainable from maleic anhydride and 1,3-butadiene. [DOS 2211408; Koppers Co., Pittsburgh, Pa.]



(1) *(2)* *(3)* *(4)*

[PR 168 IE—U]

Pyridine *(1)* **and 3-picoline** *(2)* are obtained in higher yields by the continuous gas-phase reaction of ammonia, acetaldehyde, formaldehyde, and methanol on an SiO_2/Al_2O_3 catalyst if the catalyst has a carbon content of 6—12%. The reaction

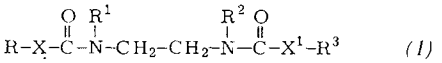
$$CH_3OH + CH_2O \rightleftharpoons CH_3OCH_2OH$$

$$NH_3 + CH_3CHO + CH_3OCH_2OH \longrightarrow \underset{(1)}{\text{pyridine}} + \underset{(2)}{\text{3-picoline}}$$

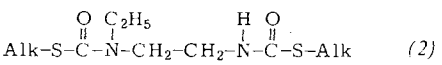
is carried out at 400—550 °C in a fluidized bed with continuous regeneration of the catalyst with air (burning off of C). The C content of the catalyst is adjusted by suitable choice of the regeneration conditions. [DOS 2203384; Rütgerswerke AG, Frankfurt]

[PR 181 IE G]

Esters of *N,N'*-ethylenedicarbamic and ethylenedithiocarbamic acids having the formula *(1)* (R, R^3 = alkyl; R^1, R^2 = H, lower alkyl; X, X^1 = O, S), in particular the compound *(2)* with



(1)

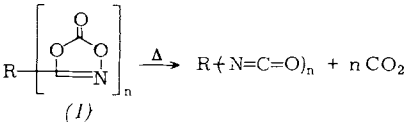


(2)

Alk = C_3, C_4-alkyl, are insect metamorphosis inhibitors similar to the natural juvenile hormone. [DOS 2324020; Stauffer Chemical Co., New York (USA)]

[PR 183 IE S]

To prepare heat-curable acrylic polymers, polyacrylic esters containing hydroxy groups are mixed with a polyfunctional 1,3,4-dioxazol-2-one (nitrile carbonate) having the formula *(1)* and cured at 120 to 150 °C. The polymers containing hydroxy groups are obtained by copolymerization of acrylic or methacrylic esters with hydroxyethyl or hydroxypropyl



(1)

(meth)acrylates. The hydroxyl values are between 20 and 150, and the acid values between 0 and 25 mg of KOH/g of substance. The preferred nitrile carbonate is adiponitrile carbonate *(1)*, R = $-(CH_2)_4-$, $n = 2$. On curing, free isocyanate groups are formed, and these crosslink with the hydroxy groups. Adiponitrile carbonate is used mainly as a crosslinking agent for acrylic varnishes. [DOS 2220806; Atlantic Richfield Co., New York (USA)]

[PR 186 IE W]

BOOK REVIEWS

Bakterien-, Phagen- und Molekulargenetik (Bacterial, Phage, and Molecular Genetics). By *U. Winkler*, *R. Rüger*, and *W. Wackernagel*. Springer Verlag, Berlin—Heidelberg—New York 1972. 1st ed., xi, 285 pp., 15 figures, stitched DM 14.80.

The present book is an attempt to fill a gap among the German-language practical textbooks for universities. It appears to me that the attempt has been successful. The book contains a large number of carefully written experimental procedures for practical courses in molecular genetics. Each experiment is preceded by an introduction giving the theoretical background. This is followed by aim, materials, procedure, evaluation, literature data, and sometimes exercises for practice (with answers). The description of the experiments is so detailed that the student can profitably work through an experiment even if he has not carried it out. Each experiment is followed by a suggestion regarding the recording of the results, a safe didactic form that can save the course supervisor a great deal of irritation, but in some cases also slightly relieves the student of the need to think over the experiment.

Besides many experiments with *Escherichia coli* and corresponding phages, the book contains a surprisingly large number of experiments with *Serratia marcescens* and Serratia phages. The main reason why so much space is devoted to this second bacterium is probably that it is one of the author's working organisms. In my opinion it would have been better from the student's point of view to extend the experiments with *E. coli*, the "pet" of molecular biologists. For example, the book fails to describe an experiment as important as the penicillin selection of auxotrophic mutants in *E. coli*. The authors are not consistent in their use of abbreviations; alongside the German DNS, RNS, *etc.*, they use English abbreviations such as EDTA and cpm. A detailed subject index should be regarded as an absolute necessity for the next edition.

The usefulness of the present book to the advanced student would undoubtedly have been increased by more frequent indications of the relationships with current research work, and not just with reviews. The book should be very useful as a German-language introduction and as a handbook for practical courses in molecular genetics. It is to be hoped that it will give many students an understanding of molecular genetics[*].

Klaus Willecke [NB 180 IE]

Koordinationsverbindungen (Coordination Compounds). By *S. F. A. Kettle*. Taschentext Vol. 3. Verlag Chemie, Weinheim 1972. 1st ed., xii, 245 pp., 106 figures and 25 tables, bound DM 16.80.

The "representative coverage" of a field of chemistry as large as modern coordination chemistry in a handy volume of the Taschentext ("pocket text") series is nowadays practically impossible without drastic limitations. The book by *Kettle*, which was first published in English in 1969 and is now available in a German translation, is thus confined mainly to the coordination chemistry of the transition metal ions, omitting all organometallic, compounds and systems containing metal ions in lower oxidation states. The book is arranged not according to groups of substances but according to general aspects such as "Nomenclature and Geometrical Structure" (Chapter 2), "Preparation" (Chapter 3), "Stability" (Chapter 4), "Crystal Field Theory" (Chapter 5), "Ligand Field Theory" (Chapter 6), "Electronic Spectra" (Chapter 7) "Magnetic Properties" (Chapter 8), "Other Methods for the Investigation of Coordination Compounds" (Chapter 9), "Thermodynamic and Related Aspects of Crystal Fields" (Chapter 10), and "Reaction Kinetics" (Chapter 11).

The author's marked interest in problems of electronic structure and static bonding in transition metal complexes can be seen *e.g.* from the fact that Chapters 5 to 8 together with the "theoretically" oriented Appendix occupy more than 125 of the 242 pages in the book, whereas the treatment of *e.g.* equally important topics of reaction kinetics and mechanisms is clearly too short, covering only 17 pages.

[*] For more advanced requirements and as a source of technical hints relating to *E. coli* genetics, see the recent work by *J. H. Miller*: "Experiments in Molecular Genetics", Cold Spring Harbor Laboratory, 1972.

While the section "Quantum-Mechanical Calculation of the Orbital Angular Momentum" has been added to the Appendix in the translation, the references to more advanced and additional literature which are given in the English version have unfortunately been omitted. The retention or the updating of these references would have helped to make the otherwise very readable book even more suitable for use as a basis of, and as supplementary reading for, lectures on coordination compounds.

R. D. Fischer [NB 184 IE]

Die Analyse der organischen Verunreinigungen in Trink-, Brauch- und Abwässern [The Analysis of Organic Impurities in Drinking Water, Water for Industrial Use, and Effluents]. By *W. Leithe*. Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart 1972. 1st ed., xii, 172 pp., 21 figs., 22 tables, bound DM 48.—

The investigation of impurities in water samples from trade, industry, agriculture, and the home is becoming increasingly important. Owing to the extreme diversity of the substances and agents with which water bodies are being increasingly contaminated, it is often necessary to limit the investigation to the determination of total contents of certain groups or to use specific methods for individual substances that are of special interest. In the present book the author tries to provide the first survey of the very topical analysis of organic impurities in water.

An introduction to the problems of the contamination of water, biological self-purification in running water, and the purification processes in clarification plants is followed by a very detailed description of methods for the quantitative estimation of classes of organic material. These include methods for the determination of organic carbon, the potassium permanganate and bichromate consumptions, and the biochemical oxygen demand. This is followed by a description of analytical methods for groups of substances and individual substances, such as fatty acids, cyanides, phenols, detergents, nitrilotriacetic acid, hydrocarbons (benzines and mineral oils), chlorinated hydrocarbons, pesticides, urea, uric acid, coprosterols, urochromes, humic acids, lignin and ligninsulfonic acids, and 3,4-benzpyrene.

With this large collection of special analytical methods for organic contaminants in drinking water, water for industrial use, and effluents, the book is a valuable addition to the standard literature on water analysis, and can be strongly recommended to all chemists concerned with the investigation and assessment of water bodies.

Dieter Eichelsdörfer [NB 193 IE]

Struktur und Reaktivität polarer Organometalle (Structure and Reactivity of Polar Organometallic Compounds). By *M. Schlosser*. Springer-Verlag, Berlin—Heidelberg—New York 1973. 1st Edit., x, 187 pp., 29 figures, bound DM 78.—.

This clearly and fluently written book deals with the structure and reactivity of organometallic compounds of alkali and alkaline earth metals. It is supplemented by a section on C—H acidities, to which a very large amount of space (64 out of 187 pages) has been devoted.

Structures in the crystal lattice, the possible aggregations of polar organometallic compounds in solution (from the dimers resulting from association *via* electron-deficient bonds to the compounds that are dissociated into metal cations and carbanions by solvation), and the connection between aggregation and reactivity are described in detail. The sections on parameters that influence reactions and on the control of reactions are particularly interesting.

Carefully chosen tables, *e.g.* the scale of "organometallically projected" C—H acidities of hydrocarbons, as well as very clear diagrams and a considerable number (447) of references even to very recent literature further increase the value of the book to the organometallic chemist who is more familiar with the other groups of the periodic system.

The book unfortunately contains a number of traps for the non-specialist and for the student; these traps are partly due to the quantitative indefiniteness of the adjective "polar", but are partly also laid by the author himself when he writes *e.g.* "the ideal case of an organometallic reaction is the carbanion process". While reading this book it would be easy to forget that it describes only one (extreme) aspect of organometallic chemistry, and the non-specialist could take the part for the whole.

With and in spite of this reservation, this is a readable, very stimulating book.

Herbert Lehmkuhl [NB 196 IE]

Techniques of Electrochemistry. Vol. 1. By *E. Yeager* and *A. J. Salkind*. Wiley-Interscience, New York—London 1972. 1st Edit., ix, 581 pp., various figures and tables, bound £ 11.70.

To forestall any misunderstandings, it should be stated that this book is concerned exclusively with electrochemical experimental and measuring techniques in the laboratory. As stated in the foreword, preparative methods and techniques for electrochemical reactions and processes will be dealt with in later volumes. Another peculiarity of this book, which is understandable in view of its American orientation, is the strong emphasis that is placed on the theoretical principles and the detailed quantitative discussion of the measuring methods described.

This is particularly noticeable in the first article, by *R. G. Bates*, on equilibrium potentials. It is not until the last few pages that the reader learns anything about the preparation of reference electrodes. However, the instructions for the platinization of platinum electrodes are not precise and therefore cannot be used, while the instructions for silver/silver chloride and calomel electrodes are unnecessarily complicated. The article by *R. Payne* on the electrochemical double layer is much more balanced. The rigid double layer is also referred to on p. 65 as the Perrin layer and on p. 72 as the Helmholtz layer. The measuring methods based on the capacity of the double layer, the surface potential, and voltammetry are described in detail, but almost exclusively for mercury electrodes. *A. Salkind* describes the measurement of the true surface area and the porosity of electrodes from a practical standpoint. The predominantly non-electrochemical methods, which are mostly described for the example of lead dioxide, can also be found in books on catalysis.

The topical field of electrochemical kinetics is finally discussed in two long chapters. *J. Kuta* and *E. Yeager* describe the stationary and non-stationary electrical methods. The relationships from the mercury drop electrode are discussed in particular detail. However, cyclic voltammetry is also touched upon. The non-electrochemical methods are summarily dealt with in the chapter by *B. E. Conway*. The emphasis here is on optical methods. The article, which was completed in 1969, naturally contains little information on fields such as ATR spectroscopy that have developed rapidly only during the past few years. Some parts of the article overlap with the chapter by *Payne*.

The book is addressed to the electrochemist, who will certainly welcome a review of measuring and experimental methods in this field. The book contains no operating procedures. Little importance is attached to experimental skill. For

example, one finds nothing about the pretreatment of solid electrodes, which is always critical. The presentation of the book is good. The typescript will probably not please everyone; it certainly does not make mathematical equations easy to read.

F. Beck [NB 197 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal.

Quantitative Thin Layer Chromatography. Edited by *J. C. Touchstone*. John Wiley and Sons, New York 1973. XIV, 330 pp., bound £ 7.50.

Environmental Phosphorus Handbook. Edited by *E. J. Griffith, A. Beeton, J. M. Spencer*, and *D. T. Mitchell*, John Wiley Sons, New York—London 1973. xvi, 718 pp., bound £ 17.50.

Electronic Structure and Magnetism of Inorganic Compounds, Vol. 2. Edited by *P. Day*. The Chemical Society, London 1973. ix, 372 pp., bound £ 8.00.—A volume in the series "Specialist Periodical Reports".

The Alkaloids, Vol. 3. Edited by *J. E. Saxton*. The Chemical Society, London 1973. ix, 337 pp., bound £ 8.50.—A volume in the series "Specialist Periodical Reports".

Organophosphorus Chemistry, Vol. 4. Edited by *S. Trippett*. The Chemical Society, London 1973. xi, 305 pp., bound £ 7.50.—A volume in the series "Specialist Periodical Reports".

Sedimentary Carbonate Minerals. By *F. Lippmann*. Vol. 6 of the series "Minerals, Rocks and Inorganic Materials". Edited by *W. v. Engelhardt, T. Hahn, R. Roy*, and *P. J. Wyllie*. Springer, Berlin—Göttingen—Heidelberg 1973. vi, 228 pp., bound DM 58.—.

Contents: Petrology; Crystal Chemistry; Calcite-Aragonite; $CaCO_3$—$MgCO_3$; From Carbonate Sediments to Carbonate Rocks.

Lehrbuch der organischen Chemie. By *H. Beyer*. S. Hirzel Verlag, Stuttgart 1973. 17th revised and expanded Edit., xx, 878 pp., bound DM 48.—.

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Separation and P **lethods, Vol. 1.** Edited by *E. S. Perry* and C. J. *van Oss*. Marcel Dekker, New York 1973. vii, 486 pp., bound \$ 22.50.

Irreversible Aspects of Continuum Mechanics Transfer of Physical Characteristics in Moving Fluids. Symposium of the International Union of Theoretical and Applied Mechanics, June 22 to 28, 1966 at Vienna. Springer, Berlin—Heidelberg—New York 1968. xii, 424 pp., bound DM 112.—.

Vom Wasser, Band 40. Issued by the Fachgruppe Wasserchemie in der Gesellschaft Deutscher Chemiker. Editor responsible for text: *W. Husmann*. Verlag Chemie, Weinheim 1973. xii, 399 pp., bound DM 78.—.

Kurzes Lehrbuch der anorganischen und allgemeinen Chemie. By *G. Jander* and *H. Spandau*. 7th completely revised edition by *J. Fenner, J. Jander*, and *H. Siegers*. Springer, Berlin—Heidelberg—New York 1973. xii, 315 pp., stitched DM 38.—

Naturally Occurring Acetylenes. By *F. Bohlmann, T. Burkhardt* and *C. Zdero*. Academic Press, London—New York 1973. IX, 547 pp., bound £ 13.—.

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The Chemistry of Natural Products VIII. Edited by The International Union of Pure and Applied Chemistry, The Indian National Science Academy (The Indian Medical Association), and The Institution of Engineers of India. Butterworths, London 1973. 177 pp., bound £ 5.25.—Plenary Lectures from the 8th International Symposium on the Chemistry of Natural Products (February 6—12, 1972, in New Delhi/India).

Atlas der Kunststoff-Analyse—Infrared Analysis of Polymers, Resins and Additives. An Atlas. By *D. O. Hummel* and *F. K. Scholl*. Vol. II: Zusatzstoffe und Verarbeitungshilfsmittel. By *F. K. Scholl*. Carl Hanser Verlag, München—Verlag Chemie, Weinheim 1973. xix, 663 pp., 30 figs., 86 tables, and 1150 spectra, bound DM 268.—.

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The Stable Isotopes of Oxygen in Research and Technical Applications

By Dieter Staschewski[*]

The stable isotopes of oxygen have proved to be efficient research tools; however, only a small fraction of the possible applications of these isotopes have been examined so far. The present progress report deals with five basic types of isotopic effects whose investigation and evaluation offer information of a new kind about physical, chemical, and biological systems and processes.

1. Introduction

The spectroscopic detection of deuterium in a residue from the evaporation of liquid hydrogen by *Urey* in 1931[1,2] was the start of a new development in research and industry that resulted in the investigation and use of the stable isotopes of the natural elements. Natural oxygen consists of three stable isotopes ^{16}O, ^{17}O, and ^{18}O, whose concentrations in atmospheric oxygen are reported to be as follows[3]:

^{16}O 99.7587 atom %
^{17}O 0.0374 atom %
^{18}O 0.2039 atom %

The isotopes of oxygen also include unstable species having the mass numbers 13, 14, 15, 19, 20, 21, 22, 23, and 24[4,5]. Among the artificially produced radioactive isotopes, ^{15}O has the longest half-life (2.1 min). The short lifetimes of the active isotopes places severe limits on their use, and investigations with the stable isotopes of oxygen are therefore much more common. In the present report the isotopes of oxygen are taken as a basis for a review of the methods and achievements of isotope research and technology. Classification of the data[6–9] leads to five fundamental types of investigations, which differ in objectives and methods. These five types are concerned with the investigation and evaluation of the following effects: 1, isotope effects; 2, fractionation effects; 3, isotopic labels; 4, nuclear and electron spin resonance; and 5, nuclear reactions.

These effects can be used as a principle for the classification of investigations with stable isotopes. Necessarily, many experiments exhibit the characteristics of several categories. For a complete survey, moreover, it would also be opportune to discuss isotope analysis and isotope preparations. These represent the basis of any isotope experiment, and consequently do not fit into the application-oriented scheme of the fundamental effects.

2. Isotope Effects

The isotopy of an element depends on differences in the numbers of neutrons and in the masses of the atomic nuclei. The differences in the atomic nuclei lead to changes in the physicochemical properties of isotopic atoms and molecules; in isotopically substituted substances and systems these changes are defined as the isotope effect. Investigations on isotope effects are mostly concerned with the relative deviations of the non-nuclear properties of the isotopically pure components. The isotope effect of isotope mixtures requires a special treatment, since it cannot always be easily deduced from the properties of the pure components.

The properties of natural oxygen and its derivatives are determined almost entirely by the isotope ^{16}O. The existence of two other stable isotopes makes oxygen a special case in

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the series of light elements up to fluorine. Pronounced deviations from the standard set by ^{16}O are to be expected in particular for ^{18}O, which is heavier by two mass units. In principle, the isotope effect in molecular systems leads to variations in the same basic information. Thus the combination of the three oxygen isotopes with the hydrogen isotopes H and D gives a maximum of nine isotopic water molecules (a total of 18 water molecules when tritium is included), and the combination with the carbon isotopes ^{12}C and ^{13}C gives a maximum of twelve stable variants of CO_2. Like the multiplicity of spectral line systems, isotopic multiplicity gives a new dimension to experimental and theoretical investigations.

2.1. Physical Properties of Isotopic Compounds

The changes in properties due to isotopy generally decrease with increasing atomic weight of the elements. Very accurate measurement is therefore usually necessary for the detection of the isotope effect in isotopic oxygen compounds. An absolute determination of the isotopic composition is essential, since the results of the measurements must be extrapolated to an isotope content of 100%.

Distinct isotope effects can be seen in Table 1 for the physical constants of water species with the isotopes H, D, ^{16}O, and ^{18}O. These differences are particularly important in connection

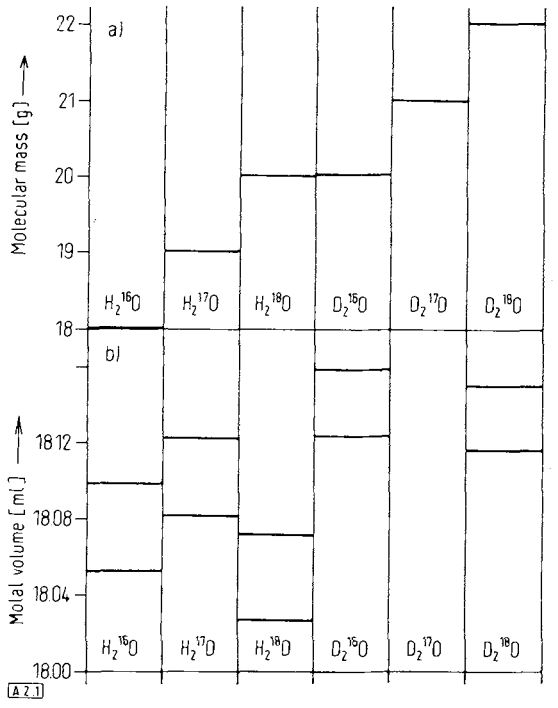


Fig. 1. a) Molecular weights and b) molal volumes of isotopic water species. Temperature dependence of the molal volume in the liquid phase: upper level 30 °C, lower level 20 °C.

Table 1. Physical properties of isotopic water species.

Property	$H_2^{16}O$	$H_2^{18}O$	$D_2^{16}O$	$D_2^{18}O$
Density at 20 °C [g/ml] [10]	0.99797	1.11064	1.10513	1.21622
Temperature of maximum density [°C] [10]	3.98	4.30	11.24	11.46
Melting point [°C] [10]	0.00	0.28	3.81	4.02
Boiling point [a] at 760 torr [°C]	100.00	100.14	101.42	101.54
Heat of evaporation [a] at 25 °C [cal/mol]	10518	10530	10868	10878
Viscosity at 20 °C [cP] [13, 14]	1.0020	1.0564	1.2471	1.3050

[a] Calculated from the vapor pressures according to [11, 12].

with the standardization of fundamental physical constants if water is used for calibration. Since natural water shows considerable variations in its D and ^{18}O contents, it is necessary to redefine the calibration basis for the liter, the g/ml density, the temperatures of 0 and 100 °C, *etc.* As a standard water, "Standard Mean Ocean Water" (SMOW), a mixture of waters taken from depth regions of all the oceans[15], has been in general use for several years. The molal volumes calculated from the densities of the isotopic water species (Fig. 1) show very great irregularity in the trend of the isotope effect; it has not yet been established which water species behaves normally and which behaves anomalously.

The substitution of a light isotope by a heavy one in a molecule leads to a shift of the lines in the Raman and IR spectra. This shift, normally taking a course toward lower frequencies, can be calculated to a first approximation by means of the Teller-Redlich product rule. Thus on replacement of the oxygen in acetone by ^{18}O, the frequency of the CO stretching vibration changes by $-23\,cm^{-1}$ ($1707 \rightarrow 1684\,cm^{-1}$) and that of the CO deformation vibration by $-14\,cm^{-1}$ ($531 \rightarrow 517\,cm^{-1}$)[16]. More pronounced isotope effects of oxygen are found in the molecular spectra of the hydrolysis products of UF_6[17,18]; thus a $\Delta\nu_s(UO)$ of $-52\,cm^{-1}$ ($893 \rightarrow 841\,cm^{-1}$) is found for UOF_4 (Fig. 2), and a $\Delta\nu_{as}(UO_2)$ of $-53\,cm^{-1}$ ($1020 \rightarrow 967\,cm^{-1}$) for UO_2F_2. The former value agrees well with the simplified product rule.

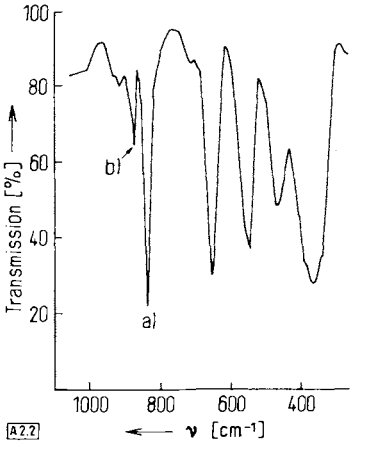


Fig. 2. Isotope effect in the IR spectrum of UOF_4 containing 90 atom % of ^{18}O (from *Jacob et al.* [17]); a) $\nu_s(U^{18}O)$, b) $\nu_s(U^{16}O)$.

In principle, the isotopic frequency shift allows a reliable assignment of the measured frequencies to certain group vibrations or normal vibrations, and is therefore of vital importance to the proof of the molecular structure. ^{18}O introduced into

a compound in the highest available concentration thus serves as an indicator for the identification of the molecular vibrations.

Table 2. Frequency anomalies in the stretching vibrations [cm^{-1}] of XO_4 anions.

Anion	State		$\nu(X^{16}O_4)$	$\nu(X^{18}O_4)$	$\Delta\nu_{exp.}$	$\Delta\nu_{calc.}$ [a]	Ref.
PO_4^{3-}	cryst.	ν_1	980	976	− 4	−56	[19]
		ν_3	1082	1037	−45		
PO_4^{3-}	aqu.	ν_1	937	947	+10	−53	[20]
		ν_3	1012	1050	+38		
AsO_4^{3-}	aqu.	ν_1	834	808	−26	−48	[21]
		ν_3	865	822	−43		
VO_4^{3-}	cryst.	ν_1	881	854	−27	−50	[21]
HVO_4^{2-}	aqu.	ν_1	873	871	− 2	−50	[21]
DVO_4^{2-}	aqu.	ν_3	854	870	+16		[22]
MnO_4^-	cryst.	ν_1	844	806	−38	−48	[23]
		ν_3	910	873	−37		
$B(OH)_4^-$	aqu.	ν_1	744	744	0	−42	[24]
		ν_3	958	982	+24		

[a] Calculated with the aid of the Teller-Redlich product rule.

A previously unknown inverse isotope effect was found by *Pinchas et al.*[19-24] in the vibrational spectra of some anions of oxo acids in aqueous solution (Table 2). On complete replacement of ^{16}O by ^{18}O, the ions $B(OH)_4^-$, PO_4^{3-}, and VO_4^{3-} exhibit a theoretically unexpected increase in the frequencies of the stretching vibrations of the tetrahedral point group or atomic grouping. Even in the cases in which the totally symmetric stretching vibration shows a negative isotope effect or no measurable effect, comparison with the calculated Teller-Redlich shift indicates that the frequency of the ^{18}O form is abnormally high. *Pinchas'* explanation for the inversion of the isotope effect is that the hydrogen bonds $X^{18}O\cdots HOH$ are weaker than the bonds $X^{16}O\cdots HOH$. The resulting anharmonicity loss produces a frequency increase counteracting the normal isotope effect. Marked anomalies have been found in several properties of the ^{18}O derivatives in a series of investigations by *Pinchas*. For example, the dimerization constant of $H_2{}^{18}O$ in dioxane is lower by a factor of 2 to 3 than that of $H_2{}^{16}O$[25].

2.2. Equilibrium Isotope Effects

In thermodynamic equilibrium, the different behavior of isotopic molecules or components causes a splitting of the equilibrium constant into a set of values lying close together. The equilibrium concentrations of the isotopic components can be replaced by corresponding partition functions according to the methods of statistical mechanics. To determine these partition functions, one must know the atomic and molecular weights, the molecular moment of inertia, and all the frequencies of the molecular vibrations. Since the spectra of gaseous compounds and their isotopic variants can be measured very precisely, statistics allows a reliable calculation of the isotope effect for gas equilibria.

Urey[26] was the first to use this principle for calculations on exchange reactions of oxygen derivatives. By elimination of the masses and moments of inertia with the aid of the Teller-Redlich product rule, *Urey* attempted to make the statistical equations simpler and mathematically more elegant. The result of such a transformation is that after all the structural terms have been eliminated, in the main only vibrational frequencies are left in the statistical formulas. However, the frequencies required for the calculation are the frequencies of a harmonic oscillator, since the product rule is valid only for harmonic vibrations. Though this model does not correspond very closely to reality, the simplified calculation procedure has become widely used. *Bigeleisen*[27,28] has applied the Urey method to condensed systems.

An important factor in the investigation of the condensed state is the vapor pressure isotope effect, which is determined either directly as the ratio p_l/p_h of the vapor pressures of the light and heavy pure components or from the difference in the concentrations of the isotopes in the gaseous and in the condensed phases at the natural isotope abundances. The vapor pressure isotope effect for the water species $H_2{}^{16}O$ and $H_2{}^{18}O$ has been measured over the range of temperatures from $+100°C$ ($p_{16}/p_{18}=1.0050$) to $-40°C$ ($p_{16}/p_{18}=1.0228$)[11,29,30].

Table 3. Vapor pressure ratios of isotopic methanol species at 760 torr (according to *Borowitz* [31]).

Isotopic variant	$\frac{p_{16}}{p_{18}}-1$	$\frac{p_{12}}{p_{13}}-1$
CH_3OH	+0.0026	−0.00028
CH_3OD	+0.0022	−0.00029
CD_3OH	+0.0017	−0.00034
CD_3OD	+0.0010	−0.00020

The vapor-pressure ratio of the isotopic methanol species (Table 3) was obtained from the enrichment of the isotopes ^{18}O and ^{13}C in the steady-state countercurrent distillation of natural methanol and its fully deuterated variant[31]. Whereas oxygen gives the normal isotope effect here ($p_l > p_h$), the inverse isotope effect ($p_l < p_h$) is found for carbon under the same conditions. The inversion of the effect is a widespread phenomenon in thermodynamic equilibria. The variation of the ratio of the equilibrium constants with temperature can sometimes be represented by a curve with several minima and maxima, which converges toward a value of unity only at very high temperatures[32].

2.3. Kinetic Isotope Effect

For quantitative predictions of the rate of a chemical reaction it is necessary to know, among other things, the energy states

of the reaction components and of the activated complex. Owing to the difficulty of the problem there is little hope for an absolute calculation of the rate constant k in most cases. A quantitative estimation of the kinetic isotope effect (k_l/k_h) seems more promising[33,34]. For the decarboxylation of malonic acid, for example, the effects of possible transition states of the reaction on the characteristics of the variation of k_l/k_h with temperature can be seen from model calculations[35]. The true kinetic isotope effect is determined either by direct measurement of the absolute reaction rates with isotopically pure substances or by measurement of the fractionation of the isotopes in a mixture of light and heavy components in the course of the reaction (competition method). The absolute method has been used for the investigation of the alkaline methanolysis of aryl benzoates *(1)*[36].

$$CH_3O^{\ominus} + C_6H_5\text{-}C(=\overset{18}{O})\text{-}OAr \longrightarrow C_6H_5\text{-}C(=\overset{18}{O})\text{-}OCH_3 + ArO^{\ominus}$$

(1)

The isotope effect, which is secondary in this case, was found to be $k_{16}/k_{18} = 1.018$ and 1.024 respectively at 30 °C[*]. According to the investigations carried out so far[37-39], the isotope ^{18}O reduces the reaction rate by 1 to 2% in the cleavage and reformation of C—O and O—O bonds. The kinetic isotope effect thus has the same order of magnitude as the $^{13}C/^{12}C$ effect in the cleavage of C—C bonds.

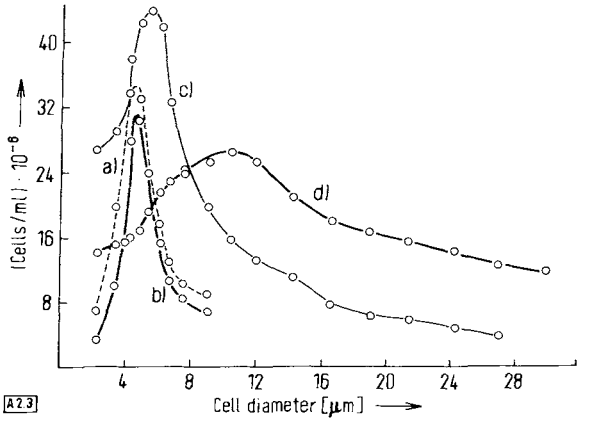


Fig. 3. Isotope effects in the size distribution of *Chlorella* cultures. a) H, ^{16}O, ^{12}C, ^{14}N; b) H, ^{18}O, ^{13}C, ^{15}N; c) D, ^{16}O, ^{13}C, ^{15}N; d) D, ^{18}O, ^{13}C, ^{15}N (from *Katz et al.* [41]).

In plant and animal organisms, there are metabolic processes consisting of large numbers of chemical reactions with steps which must all be correctly timed in relation to one another. The extent to which kinetic isotope effects of oxygen influence or can be used to influence the synchrony of the vital processes is still largely unknown. For bacteria *(Escherichia coli)* grown in $H_2{}^{18}O$, the exponential growth was found to be slower by a factor of 1.5 than the normal growth in natural water ($H_2{}^{16}O$)[40]. For unicellular algae *(Chlorella vulgaris)*, culture in $D_2{}^{18}O$ led to an unusual increase in the average cell size and in the range of variation of the cell size (Fig. 3)[41]. However, no toxic effects of heavy oxygen were observed on replacement of ^{16}O by ^{18}O in the bodies of living mice[42]. The development of the new field of isotopic biology is of great importance to the medical applications of the oxygen isotopes, which have already been put into practice with the use of $C^{18}O$ in lung function tests[43].

[*] An isotope effect is described as secondary if bonds from the isotope are not broken at all or are not broken in the rate-determining step. The value $k_{16}/k_{18} = 1.018$ refers to *p*-bromophenyl benzoate and the value 1.024 to phenyl benzoate.

2.4. Theoretical Evaluation of Isotope Effects

The question of the advantage that can be gained from the measurement of isotope effects in connection with the understanding of natural processes leads to a problem that has recently become increasingly important. The quantitative agreement of the measured isotope effects with the calculated values should be the ultimate criterion for the validity of a theory, whether in the theoretical treatment of anharmonic molecular vibrations or in the model of a liquid structure. Thus the isotope effect in the viscosity of isotopic water species has been studied to check *Eyring*'s theory[13,44].

So far, however, theoretical expectations have only been partly satisfied. The only basis for the evaluation of the isotope effect appeared to be the postulate of the absolute equality of the force fields and electronic structures in isotopic systems. The Born-Oppenheimer approximation, according to which the potential energy of the nuclear motion and the molecular force constants are independent of the isotopic substitution, is regarded as an axiom in particular by *Bigeleisen* and his school[45a]. *Steele*[45b], on the other hand, points out that systems involving polyatomic molecules correspond to complicated many-body problems, in which isotope-dependent potential components of the anharmonic vibrations always occur. According to *Steele*, the physical properties of liquid CH_4 and CD_4 can best be represented by slightly modified potential functions. The "anomalous" isotope effects discovered by *Pinchas*[19-25] for heavy oxygen now satisfactorily show that this assumption of the equality of potentials has no absolute validity. The frequency increases resulting from substitution with ^{18}O in phosphate and borate can only be explained on the basis of changes in potential energy.

New anomalies are also being found in growing numbers for other elements. *Wicke et al.*[46] have reported an unexpected course for the isotope effect in the diffusion of the hydrogen isotopes in palladium. The diffusion coefficient D decreases in the order $D_D > D_H > D_T$. A quantitative analysis of true isotope effects without the use of simplifying basic assumptions is certainly difficult. The Born-Oppenheimer approximation may still be useful, *e.g.* in the form of the Teller-Redlich product rule, if it is used as a reference scale for assessing of the true course of the potential.

The total energy of a molecular system can be resolved into translational, rotational, and vibrational components. If a property of the system is caused primarily by translation processes, the isotope effect depends mainly on the molecular weights, as is found for the vapor pressures and viscosities of the isotopic water species. The anomalous behavior of the molal volume, on the other hand, points to strong vibrational components in the statistical energy distribution of the associated water molecules. The multi-body effect of the molecular vibrations, which should be exaggerated in the condensed phase, is evident even for the isolated single molecule. The anharmonic interaction between the fundamental of the symmetric stretching vibration and the first harmonic

of the deformation vibration leads to a characteristic double line in the Raman spectrum of carbon dioxide, for which *Fermi* was the first to find an explanation. On attempting a quantitative treatment of the isotope effect of the Fermi resonance, one will discover the complete failure of the conventional models[47]. Analysis of the accurately recorded vibrational spectra of the isotopic CO_2 variants in the gas phase showed that the perturbation constant W_0 increases with decreasing mass of the central atom and with increasing mass of the outer atoms:

$$W_0(^{13}C^{16}O_2) < W_0(^{12}C^{16}O_2) < W_0(^{12}C^{18}O_2)$$

In order to establish an empirical law for this mass dependence, it was necessary to assume that the real cause of the isotope effect is not the change in the angle of the CO_2 molecule but the motion of the central atom[47].

3. Fractionation Effects

Because of the differences in the properties of isotopic substances, all transformations or transitions of the substances are accompanied by temperature-dependent fractionations of the isotopes. The elementary effect of this isotope separation is expressed quantitatively by a separation factor α, which is defined for the oxygen isotopes ^{16}O and ^{18}O by

$$\alpha_{18} = \left(\frac{[^{18}O]}{[^{16}O]}\right)_A \Big/ \left(\frac{[^{18}O]}{[^{16}O]}\right)_B$$

and which gives the ratio of the isotope concentrations in the phases or chemical compounds A and B. For simple systems, the separation factor can be correlated with the equilibrium constants and calculated by the methods of statistical mechanics. In the vaporization equilibrium, the distillation separation factor corresponds to the ratio of the vapor pressures of the pure isotopic components, provided that the latter form ideal mixtures and satisfy *Raoult*'s law and *Dalton*'s law of partial pressures. The investigation of the fractionation effects can be used for the determination of "pure" isotope effects, but is more important as a basis for the estimation of paleotemperatures, for the differentiation and characterization of chemically identical substances, and finally for the purification of the isotopes.

The elementary effects of oxygen are attracting increasing interest in physical chemistry. Examples from this field are the investigations on the electrolytic evolution of gaseous oxygen[48] and on the bonding of crystal water in copper sulfate[49]. The fractionation of the oxygen isotopes during the evolution of photosynthetic oxygen in transpiring leaves has recently been studied to explain the anomalously high ^{18}O content of atmospheric oxygen (Dole effect)[50]. The measurement of $^{18}O/^{16}O$ fractionation effects has already become routine in hydrology and geology.

3.1. Fractionation Effects in the Natural Water Balance

The range of variation of the ^{18}O content in natural water is roughly given by the marginal values of 0.199 atom % (ocean bottom water) and 0.189 atom % (polar ice)[51]. Since the isotopic composition of water depends on latitude, elevation, time of year, climate, and other factors, it is a valuable indicator in the study of hydrologic systems. The necessary isotope analyses call for the measurement of minute changes in the ratios $R_{18}=[^{18}O]/[^{16}O]$ and $R_D=[D]/[H]$. The isotope fractionation is expressed internationally by the δ notation as the $^0/_{00}$ deviation in relation to SMOW (Standard Mean Ocean Water):

$$\delta[^0/_{00}] = \left(\frac{R}{R_{SMOW}} - 1\right) \times 1000$$

In mass-spectroscopic analyses using the double-collector technique, one can achieve an accuracy of $\Delta\delta_{18} = \pm 0.1\,^0/_{00}$ or $\Delta[^{18}O] = \pm 0.00002$ atom % and $\Delta\delta_D = \pm 1\,^0/_{00}$ or $\Delta[D] = \pm 0.000015$ atom %[52]. As a result of evaporation and condensation, the water circulating on the terrestrial sphere undergoes a succession of fractionation processes, which are strongly temperature-dependent. In the course of these processes the individual isotopes are fractionated to varying degrees. According to *Craig*[53], the following relation is generally valid for atmospheric precipitation:

$$\delta_D = 8\delta_{18} + 10$$

Under favorable conditions, the evaluation of the δ_D and δ_{18} values of water and ice samples allows the determination of the temperature variation during condensation. Thus the formation and growth of hailstones has been investigated by analysis of the radial distribution of hydrogen and oxygen isotopes (Fig. 4)[52]. The measurement of the δ_{18} and δ_D values is used in ground-water hydrology for the differentiation of bodies of water, and for the elucidation of the relationships between springs, lakes, and ground-water reservoirs, and for the determination of water balances for standing and flowing bodies of water[54].

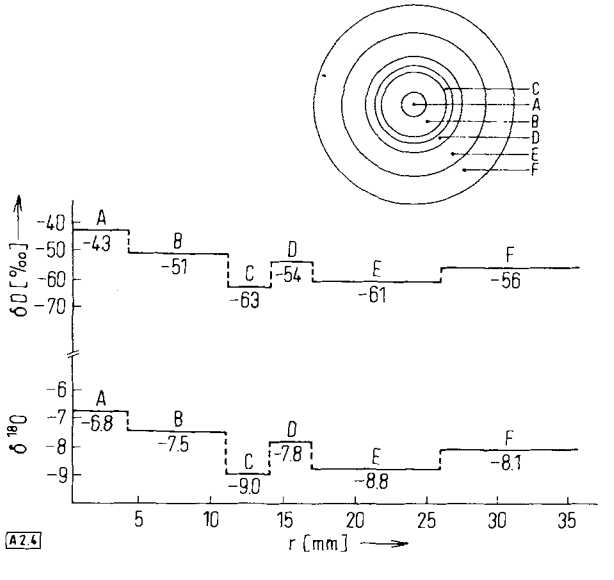


Fig. 4. Radial distribution of deuterium and ^{18}O in a hailstone (from *Majoube et al.* [52]).

3.2. Fractionation Effects in Geochemical and Cosmochemical Processes

Marine deposits of calcium carbonate shells of belemnites, mollusks, and foraminifera exhibit periodic variations of the

$^{18}O/^{16}O$ ratio, which are due to temperature differences at the time of formation of the calcium carbonate. The isotopic composition of the limestone oxygen functions here as a thermometer, which can be calibrated by means of the temperature dependence of the equilibrium constant for the exchange reaction

$$CaC^{16}O_3 + H_2{}^{18}O \rightleftharpoons CaC^{18}O^{16}O_2 + H_2{}^{16}O$$

It is found[55,56] that:

$$T[^\circ C] = 16.5 - 4.3(\delta_{18}^{limestone} - \delta_{18}^{water}) + 0.14(\delta_{18}^{limestone} - \delta_{18}^{water})^2$$

The temperature determination, which can achieve an accuracy of at best $\pm 0.5\,^\circ C$ with an accuracy of $\pm 0.1\,‰$ for δ_{18}, in principle presupposes that the ^{18}O content in the prehistoric oceans is known. By careful elimination of misleading factors, however, absolute paleotemperatures can be extrapolated with an accuracy of 5 °C, the lower time limit being roughly the beginning of the Mesozoic. With this method it has been possible to trace the temperature cycles of the ice ages back over a period of approximately 150 million years (Fig. 5)[57].

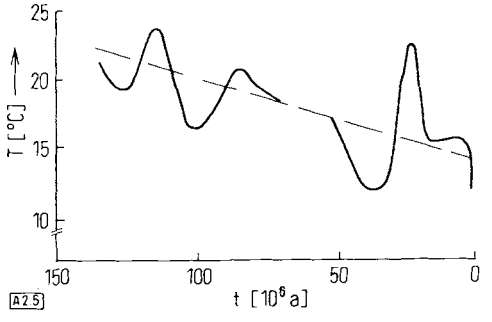


Fig. 5. Temperature variations in middle latitudes during the past 150 million years according to the isotope analysis of marine calcium carbonate [57].

The equilibrium distribution of the isotopes ^{16}O and ^{18}O in the calcite/water system has been the subject of very intensive experimental studies between 0 and 760 °C, and has been used for geothermometry. Other isotope thermometers[55] are based on the $^{18}O/^{16}O$ fractionation effect in the systems quartz/water (250—800 °C), magnetite/water (400—800 °C), and muscovite/water (400—650 °C)[58].

"Internal" thermometers are obtained from the combination of two solid phases after elimination of the aqueous phase. The quartz/magnetite pair has proved to be particularly reliable, whereas no satisfactory establishment of the isotope equilibrium is found for other pairs. Thus if quartz and magnetite or other suitable pairs of minerals are present in a rock, the formation temperature can be determined directly without any information about the gaseous or liquid phase.

Definite systems of substances that can be used for the quantitative evaluation of the fractionation effect are not always present. In general, however, the isotope method is an excellent means for the establishment of genetic relationships between minerals and for determining whether a silicate was formed at high or at low temperatures. The extension of the isotope method to the investigation of meteorites and moon rock[59] leads to the "cosmothermometer", with the aid of which conclusions can be drawn about the formation of planets and moons from interstellar dust and gases[60]. *Clayton et al.* recently found virtually pure ^{16}O in dust particles from the Allende meteorite. This could mean that the solar system is older than is currently believed[61].

3.3. Multiplication of Elementary Fractionation Effects in Technical Isotope Separation Plants

The elementary effect that results in a slight enrichment of an isotopic component in one phase or the other in the thermodynamic equilibrium of two phases is the basis of the method used to obtain the pure oxygen isotopes. The separation processes carried out so far on the technical scale utilize the countercurrent flow between a liquid phase and a gaseous phase, or in the case of thermodiffusion, the countercurrent flow within a gaseous phase (Table 4). With phase reversal at the ends of a separation section, the countercurrent principle leads to multiplication of the elementary fractionation effect, the separating effect of a countercurrent column being measured by the number of theoretical plates.

A theoretical plate, which is defined by a concentration shift corresponding to the elementary separation factor along the separation column, is realized by a column section of a certain height (HETP). Since the elementary effects of the $^{18}O/^{16}O$ and $^{17}O/^{16}O$ separations are very small, the process with the highest separation factor and the smallest HEPT should be the most suitable for the isolation of the oxygen isotopes. The highest separation factor is found in the exchange equilibrium between gaseous CO_2 and water[62]. However, because the exchange proceeds slowly even at high temperatures and in the presence of catalysts, technically acceptable values for the HEPT were not achieved[63]. According to the selection

Table 4. Parameters of the $^{18}O/^{16}O$ and $^{17}O/^{16}O$ separation in technical isotope separation plants. T = working temperature, α = separation factor, HETP = height of a column section corresponding to one theoretical plate.

Process	T [°C]	α_{18}	α_{17}	HETP [cm]	Ref.
H_2O Distillation	+ 77—79	1.0061	1.0032	1.6—2.5	[70]
D_2O Distillation	+ 75	1.0051	1.0026	1.5—2.5	[73]
CO Distillation	−192	1.008	1.004	1.6	[68]
NO Distillation	−152	1.0372	1.0186	1.4—3.8	[64]
$NO/H_2O/HNO_3$ Exchange	+ 25	1.018	1.009	3.7	[66]
CO_2/H_2O Exchange	+ 25	1.042	1.022	*ca.* 600	[63]
	+120	1.024	1.013	*ca.* 17	
O_2 Thermodiffusion	+800/50	1.016	1.008	2.8	[70]

criteria mentioned, therefore, the most favorable process appears to be the countercurrent distillation of nitric oxide, though this calls for an unconventional low-temperature technique. An NO distillation plant with packed columns has recently been set up at Los Alamos; the columns, sunk to a depth of 200m in the ground, are operated at about -150 °C. The plant is designed for an annual isotope output of 12 kg of ^{18}O, 2 kg of ^{17}O, and 18 kg of ^{15}N[64,65].

The possibility of separating oxygen and nitrogen isotopes at the same time also characterizes the Spindel-Taylor process, which is based on the reaction of nitrogen oxides with nitric acid[66]. However, this process seems to be employed for the concentration of ^{18}O only in Tbilisi (USSR)[67]. The low-temperature distillation of carbon monoxide[65,68], which is used for the $^{13}C/^{12}C$ separation, also finds little application for the production of the oxygen isotopes.

The separation process that is of the greatest practical importance at present is the one with the lowest separation factor and the simplest procedure, *i. e.* the countercurrent distillation of water[69]. In this field the Weizmann Institute long held a dominant position. The distillation plant at Rehovot (Israel) has been on stream for several years under steady-state conditions, *i. e.* the input of feed and the removal of product (about 5 kg of ^{18}O with a purity of 98 atom % annually) are performed continuously with constant concentration profiles[70,71]. The ^{17}O intermediate product, which is withdrawn with a ^{17}O concentration of 20 atom %, is partly decomposed by electrolysis and passes in the form of gaseous oxygen into an arrangement of thermodiffusion columns, where it is concentrated up to 96 atom % of ^{17}O. The same principle was used in a ^{17}O separation unit in Oak Ridge[72], which has now been closed down. A particularly promising variant of water distillation is being pursued at the Nuclear Research Center in Karlsruhe. Instead of natural water, the feed material here is the heavy water produced for nuclear reactors, which not only has a high deuterium content but also exhibits a considerable pre-enrichment in ^{18}O and ^{17}O[73,74].

The separation plants being used for the production of pure oxygen isotopes are all experimental plants that have been built by research institutes or research centers and in which economic aspects were of secondary importance. When all these plants have reached full production, a total annual output of 5—6 t of ^{16}O, 20—22 kg of ^{18}O, and 2—3 kg of ^{17}O can be expected. The quantities of oxygen isotopes produced in this way are still very small in comparison with the production of D_2O, but they will allow a more liberal use of these isotopes in research and technical fields than has been possible for a long time.

4. Isotopic Labels

An important class of applications for the oxygen isotopes depends on the possibility of distinguishing between the isotopes of the same chemical element. If a component of a reaction is labeled with an isotope enriched beyond its natural abundance, its behavior in the reaction can be followed qualitatively and quantitatively. The significance of this effect is said to be summed up by *Seaborg* in the following words[75]: "The possibilities for learning that have been offered to science by the discovery of the principle of labeled atoms are comparable in their importance only with the invention of the microscope".

In practice, the principle of labeling with isotopes can be applied in three ways. By the use of *tracers*, it is possible to study the course of a reaction in detail and to elucidate reaction mechanisms. Labeling of selected components and investigation of the *isotope exchange* allows the direct measurement of the formation and decomposition of molecules and the self-diffusion of the atoms of an element. The *dilution method* allows the quantitative determination of components of a reaction mixture without complete separation.

The tracer method utilizes the disequilibrium between both the chemical components and the isotopes, whereas in the isotope exchange reactions the chemical components are in thermodynamic equilibrium, but the isotopes are not. In the dilution method, both chemical equilibrium and equilibrium between the isotopes must be established.

4.1. Stable Tracers

The history of the stable tracer isotope ^{18}O began in 1934, when *Polanyi* and *Szabo*[76] found, in the alkaline hydrolysis of amyl acetate *(2)*, $R=CH_3$, $R'=C_5H_{11}$, in ^{18}O-water, that heavy oxygen had been transferred into the acetic acid, but not into the amyl alcohol. This proof of the alkyl oxygen mechanism[48] for the hydrolysis of esters pointed the way for the development of theoretical organic chemistry (Fig. 6).

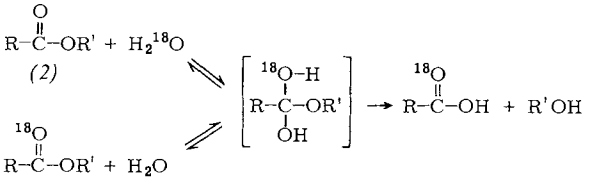


Fig. 6. Mechanism of hydrolysis and oxygen exchange in esters of carboxylic acids.

It was also established by labeling with ^{18}O that the oxygen of the amide in the Beckmann rearrangement of ketoximes comes from the water. There have been so many tracer experiments in inorganic chemistry that we shall merely refer here to the exemplary investigations by *Taube*[48,77], who explained among other things the transfer of oxygen from ozone to SO_2, NO_2^-, Mn^{2+}, and Tl^+, and to *Gordon*'s work[78] on the redox reaction of U^{IV} with Cl^{III}. In the latter case the importance of the tracer is that it enables one to distinguish between $1e^-$ and $2e^-$ transitions.

The application of heavy oxygen in biochemistry precipitated some revolutionary changes in this field[79,80]. The discovery of the oxygenases in 1955 by tracer experiments with labeled oxygen gas marked the end of the Wieland theory, according to which molecular oxygen merely acted as a secondary electron acceptor in the biological oxidation processes. Following the pioneering work of *Mason*[81] and *Hayaishi*[82], an immense number of enzymes capable of transferring atmospheric oxygen directly to the metabolic substrates have been discovered. The inert behavior of molecular oxygen toward exchange reactions proved to be a favorable precondition in these investigations.

In-vivo experiments with oxygen isotopes are often complicated by the fact that the isotopic label is broken down too rapidly by oxygen exchange with the ever-present cell water, which is usually also catalyzed by enzymes. The undesirable isotope exchange is further favored by relaxation effects, which result from the hindrance of mass transfer by the numerous cell membranes and from the ability of the cells to store metabolites. *In-vitro* experiments therefore give more reliable results, but they cannot be carried out in most cases. This problem is particularly evident in plant photosynthesis.

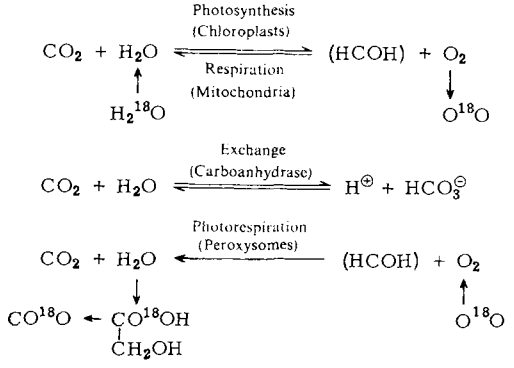


Fig. 7. Fundamental balances of the oxygen turnover in the photosynthesis of plants.

Plants use water and carbon dioxide as starting materials for the biosynthesis of carbohydrates and the production of molecular oxygen (Fig. 7). An attempt to answer the question whether the oxygen formed by photosynthesis comes from the water or from the CO_2 was made as early as 1941 by ^{18}O labeling experiments, which indicated that it comes from the water[83]. Unfortunately it was not taken into account that the oxygen exchange between H_2O and CO_2, additionally accelerated by the enzyme carboanhydrase, leads to very rapid leveling of the ^{18}O concentrations, and that the water, which is present in by far the greater quantity, then determines the ^{18}O level in the evolved oxygen gas. Despite many recent investigations on the photosynthesis mechanism, the source of the photosynthetic oxygen has not yet been established[84,85]. It is certain, however, that if a conclusive answer is possible, it can only be provided by isotope experiments.

Biochemical research is being concentrated at present on special steps in photosynthesis. Thus it has been found with the aid of the tracer technique that the carotenoid pigments in the chloroplasts, particularly the xanthophylls, are involved in the evolution of oxygen[86]. ^{18}O also supplies proof that considerable oxygen absorption occurs during active photosynthesis[87]. The oxygen taken up by the peroxysomes is consumed in the simultaneous photorespiration.

The increasing use of the heavy isotopes of oxygen in the investigation of animal and human metabolism also merits attention. The mechanism of the enzymatic transformation of a carcinogenic substance has been established by an *in-vitro* experiment[88]. The process in question is an isomerization of 2-fluorenyl-*N*-hydroxyacetamide, which is converted into the corresponding *o*-amidophenol by an enzyme system isolated from the microsomes of rat liver.

Samuel et al.[89,90] examined the direct conversion of oxygen gas into CO_2 and water in the brains of living rats. The *in-vivo* isotope analysis was made possible by implanted microprobes. These contained replaceable tantalum wires, which were anodically oxidized by a pulse of current, and the surface oxide was then examined for ^{18}O and ^{16}O by activation analysis (see Section 6.1). The tracer experiments showed that in deep anesthesia the oxygen turnover in the brain cells of the animals decreases by 20% in relation to the normal sleeping value, while it increases by 20% in stress situations. A half-life of about 50 h was found for the water metabolism in rat brain. The respiratory oxygen absorbed by the brain cells maintains several metabolic processes, including the stepwise conversion of phenylalanine into dopamine, which plays an important part in the central nervous system as a neurotransmitter. In order to detect the formation of dopamine in specific regions of the brain, it was necessary to dissect and extract the rat brains. The use of the isotope ^{17}O as a biological tracer was found to be very advantageous for the isotope analysis of the micro quantities of organic material extracted. The ^{17}O, which was administered to the animals in a high concentration in the respiratory oxygen, could be quantitatively determined in the isolated metabolic products by neutron activation.

4.2. Exchange Reactions

The exchange of isotopes between like or unlike molecules is clear proof of the limited lifetimes of chemical bonds. It allows a quantitative determination of reaction kinetics, and particularly the determination of the activation energies of physicochemical processes. The accuracy of such measurements depends to a small extent on the consideration of isotope effects.

Exchange reactions of the oxygen isotopes have been investigated in homogeneous and heterogeneous systems in all aggregation states. The homomolecular oxygen exchange in the gas phase reaches measurable values only above 200 °C[91]. It is accompanied by a heterogeneous exchange between the O_2 gas and the oxide surface of the reaction vessel, which increases rapidly with rising temperature. Far more than 100 publications have been devoted to the heterogeneous exchange between gaseous oxygen and solid oxides[92,93]. It was hoped that the nature of oxide catalysts might be elucidated by this method. Though exchange studies have made important contributions to our understanding of the solid aggregation state, they have not been able to reveal any direct relationship between the exchange rate and activation energy on the one hand and the catalytic activity on the other. The mobility and self-diffusion of oxygen in oxide layers[94,95] on metal surfaces and in oxide ceramics (UO_2)[96] can also be studied with the aid of the stable tracers ^{18}O and ^{17}O.

A focus of great interest in isotope research is the oxygen exchange between organic and inorganic compounds and the solvent water. Since oxygen is an extremely reactive element, there is only a small number of oxygen derivatives that do not exchange oxygen with water under normal conditions[3,97]. These include the anions of the salts $KClO_4$, $KClO_3$, KNO_3, KNO_2, Na_3PO_4, Na_3PO_3, Na_2SeO_4, Na_2SO_4, Na_2SO_3, Na_2CO_3, and CH_3COOK. Acidification of solutions of the salts is enough to induce the exchange process. The only organic oxygen compounds that are resistant to oxygen exchange with water are the normal monohydric or polyhydric alcohols such as methanol and glycerol and the monohydric

and polyhydric phenols. Tertiary alcohols and hydroquinone are again able to undergo the exchange. The resistance of alcohols and phenols has been used for the detection of methoxy groups that had been introduced biosynthetically into the benzene ring[98].

The inability of alcohols to undergo oxygen exchange was also an important part of the argument in the case of the hydrolysis of esters. The acyl-alkoxy cleavage can be demonstrated here beyond any doubt, though isotope exchange between the carbonyl oxygen and the water occurs simultaneously with the hydrolysis of the ester (Fig. 6). Both reactions proceed *via* the same intermediate[97]. Which of the two is faster depends on the pH of the solution and on steric and electronic factors.

The oxygen exchange between carbon dioxide and water, which is due to the formation and decomposition of carbonic acid and of hydrogen carbonate ions, has repeatedly been investigated by the ^{18}O labeling method[99-101]. The kinetic constants of the carbonic acid and hydrogen carbonate reaction as calculated from the exchange rate give a valuable addition to the data obtained by conventional measuring methods, which exhibit considerable divergence. The superiority of the isotope method is seen above all in the measurement of the carboanhydrase activity. Even extremely small quantities of the enzyme can be detected in this way in plant, animal, or human cell tissue[102].

The exchange kinetics with heavy oxygen have also been measured in other systems, *e. g.* in solutions of bromate ions in H_2O and D_2O[103,104]. A photochemically induced oxygen exchange was observed in chemically pure acetone doubly labeled with D and ^{18}O[105].

4.3. Dilution Method

The use of compounds with enriched isotopes for the quantitative chemical analysis of substances that are difficult to isolate is based on a simple principle. A mixture containing a substance A in a molal quantity M with an isotope having the natural abundance c_0 is mixed with a small quantity M' of the same substance A having an isotope concentration c' and allowed to come to general equilibrium. By isolating any fixed quantity of A from the mixture and determining the new isotope content c, one can easily calculate the total quantity M of the substance A with the aid of the mass balance

$$Mc_0 + M'c' = (M + M')c$$

as follows:

$$M = M'(c - c')/(c_0 - c)$$

An example of the application of this principle has been described by *Tamada* and *Furuya*[106]. The oxygen content of steel is usually determined by a vacuum melting technique. It was possible to save a platinum metal bath required for this determination by the use of the isotope method. The exchange of the oxygen in the molten metal with the ^{18}O in a fixed quantity of CO gas led to a measurable decrease in the isotope content, from which it was easy to find the desired oxygen content.

5. Nuclear and Electron Spin Resonance

Among the three stable oxygen isotopes, only the middle one, ^{17}O, has a nuclear spin, which is accompanied by a magnetic moment (nuclear angular momentum quantum number $I = 5/2$). The ^{17}O nucleus also has an electric quadrupole moment. The quantization of the nuclear spin in a magnetic field allows the measurement of characteristic energy states, which provide important information about the embedding of the nucleus in an atomic or molecular structure. The shielding effect of neighboring electrons leads to a "chemical shift" of the ^{17}O resonance line, which, when measured as a relative change in the magnetic field, extends over a range of about 1000 ppm. This effect is about 100 times as large as for proton resonance. The spin-spin coupling between like or unlike nuclei and between nuclei and unpaired electrons causes line splitting, whose multiplicity ($Z = 2NI + 1$) allows conclusions to be drawn about the structure and number of electronically equivalent nuclei. The number, position, and width of the resonance lines are closely related to the mean lifetimes of the molecular states, with the result that the substitution and exchange kinetics can be quantitatively determined.

5.1. Chemical Shift and Structural Problems

The chemical shift of the ^{17}O resonance signal of oxygen compounds is generally measured in relation to the line of $H_2{}^{17}O$. The position of a ^{17}O line in the NMR spectrum is characteristic not only of a certain type of bonding of the oxygen atom but sometimes even of the particular functional group[107]. Thus aldehydes and ketones dissolved in water give ^{17}O shifts from -50 to -70 ppm for the OH groups of the acetal and about -520 to -570 ppm for the double-bonded oxygen in the CO group (Fig. 8).

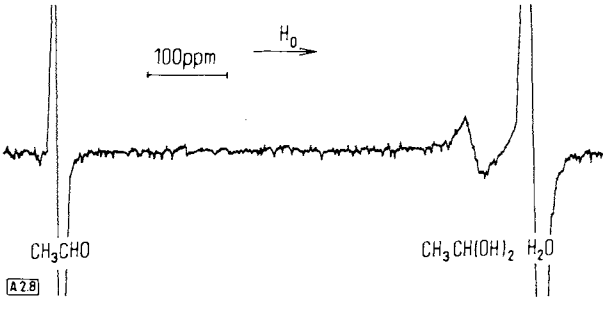


Fig. 8. Chemical shifts of ^{17}O-NMR signals in a solution of acetaldehyde in ^{17}O-water [107].

A series of NMR studies have been devoted to the solvation of cations and anions. Provided that the water of hydration is bonded strongly enough to a central ion and undergoes only a slow exchange with the free bulk water, it is represented in the spectrum by a specific signal that stands out from the ^{17}O signal of the solvent. By measurement of the intensities of the separate signals, coordination numbers of 6, 4, and 6 were found for the hydration complexes of the ions Al^{3+}, Be^{2+}, and Ga^{3+} respectively[107]. The above conditions are not satisfied in 1:1 electrolytes. These give only one ^{17}O signal, which results from the superposition of many short-lived solvation states and shows a shift that is proportional to the concentration of the salt[108].

5.2. Reaction Kinetics

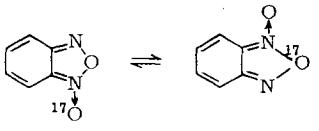
There are two ways of following kinetic processes by NMR spectroscopy. Which of these is used in a given case depends on the absolute value of the reaction rate. For processes having a half-life of more than 1 min, the change in the concentration of a ^{17}O-labeled component can be determined directly from the change in the signal intensity. For example, the reversible hydration of aliphatic aldehydes and ketones *(3)*,

$$>C=^{17}O + H_2O \rightleftharpoons >C\begin{matrix}{}^{17}OH\\OH\end{matrix} \rightleftharpoons >C=O + H_2{}^{17}O$$

(3)

which proceeds in accordance with the indicated reaction scheme in the case of ^{17}O-labeled compounds, can be pursued by direct measurement of the CO resonance line. Half-lives of between 6 min and 2 h were found[109,110].

For fast reactions with half-lives of between 1 and 10^{-3} s, the kinetics are determined by analysis of the excess width of the resonance lines. A good example of this technique, which is still little used in ^{17}O measurements, is the intramolecular rearrangement of benzofurazan oxide *(4)*[111].



(4)

The heterocycle has two chemically non-equivalent oxygen atoms, for which two different ^{17}O resonance lines are found at room temperature. With rising temperature these signals become broader and broader until they finally combine to form a new signal, which dominates the spectrum at 100 °C. The intramolecular oxygen exchange is then so fast that the ^{17}O resonance responds only to a mean value of the electron density in the molecule.

5.3. Nuclear Spin/Electron Spin Interaction

In free radicals, coupling occurs between the spins of the unpaired electrons and the nuclear spins. Measurement of the electron spin resonance (ESR) reveals a hyperfine structure of the resonance line in this case. The interaction of an electron with one ^{17}O nucleus leads to six ESR lines, and with two ^{17}O nuclei, as in $^{17}O_2$, to a total of eleven ESR lines. This fine structure is a reliable means for the identification of oxygen atoms in the ESR spectrum and for the selective investigation of their electronic states. The formation of the O_2^- radical in redox processes has been detected by the ESR technique. On oxide surfaces exposed to γ radiation, *Tench et al.*[112-114] obtained the ESR spectra of the species O^-, O_2^-, and O_3^- in the adsorbed oxygen (Fig. 9). It was found that the radical $(O^-)_s$ reacts readily with excess molecular oxygen to form the molecule-ion $(O_3^-)_s$, which changes into $(O_2^-)_s$ above 400 °C. This last species is stable at room temperature and resistant to isotope exchange with the oxide ions of the lattice.

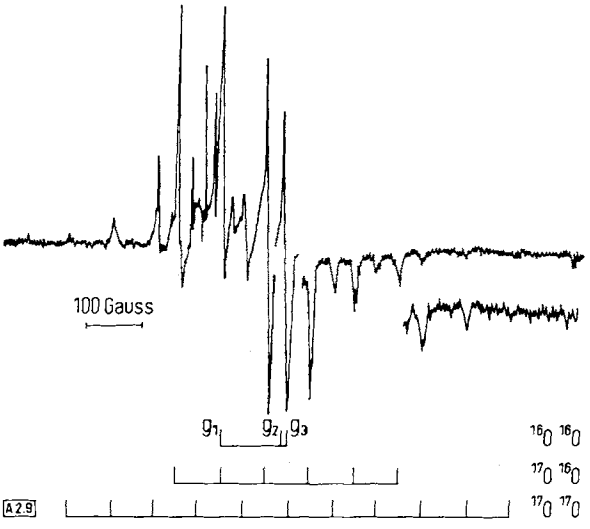


Fig. 9. Fine structure of the ^{17}O electron spin resonance line of molecular oxygen on MgO having a large specific surface area (from *Tench* [114]).

6. Nuclear Reactions

The specific nuclear reactions of the oxygen isotopes proceed regardless of the chemical or physical form in which the oxygen is present. An oxygen isotope may be used as an accelerated projectile or as a stationary target. The nuclear processes with high-energy ^{16}O and ^{18}O ions will not be discussed here because of their small range of applications. Target reactions are important in practice, particularly irradiation experiments with neutrons and with charged elementary particles. Whereas the uncharged neutrons penetrate massive samples of material and cause total activation, projectiles such as the proton, the deuteron, the triton, and the α particle have only a very small penetration depth because of their electric charge, and activation with these particles is confined to surface layers. The transformation and decomposition products formed in the nuclear reactions are also strongly absorbed by the sample if they carry a charge. For this reason, neutron activation is mainly followed by measurement of the γ radiation, which is either emitted promptly or given off by a reaction product after a certain delay.

6.1. Activation Analysis

The conventional isotope analysis of oxygen is carried out in special cases by densimetric methods[115,116], but generally with the mass spectrometer[117,118]. Though quantities of the order of 1 mg to 10 µg can sometimes be determined by direct mass-spectrometric measurement, nuclear activation analysis[119] has definite advantages to offer in trace analysis. A series of nuclear processes, involving a considerable amount of experimental work, is available for use in activation analysis (Table 5).

The (α,n) process[120] has low cross sections, but is relatively simple to use. Unstable isotopes of the elements Ra, Rn, Po, Ac, Am, Pu, *etc.* are used as α sources. In the case of the heavy oxygen isotopes, α capture leads to the formation of stable neon isotopes, and the emitted neutron or γ radiation can be measured. Differentiation between ^{18}O and ^{17}O is possible only by γ spectroscopy. An arrangement for the measurement of neutrons with the aid of BF_3 proportional

Table 5. Nuclear reactions and activation analysis of the stable oxygen isotopes.

Isotope – nuclear reaction —product	Cross-section	Excitation energy	Half-life of product	Decay radiation of product	Detection limit of isotope
$^{18}O(\alpha,n\gamma)^{21}Ne$	60 mb ($\bar{\sigma}$)	5—6 MeV			0.1 mg
$^{17}O(\alpha,n\gamma)^{20}Ne$	60 mb ($\bar{\sigma}$)	5—6 MeV			
$^{18}O(p,n)^{18}F$	200 mb	4 MeV	112 min	$\beta^+ \rightarrow \gamma$	10^{-8} mg
$^{17}O(p,n)^{17}F$		4 MeV	66 min	$\beta^+ \rightarrow \gamma$	
$^{18}O(p,\alpha)^{15}N$	75 mb	0.7 MeV			10^{-9} mg
$^{16}O(d,p)^{17}O$	40 mb	0.9 MeV			10^{-8} mg
$^{18}O(n,\gamma)^{19}O$	0.2 mb	thermal	29 s	β^-, γ	2 mg
$^{17}O(n,\alpha)^{14}C$	235 mb	thermal	5568 a	β^-	
$^{17}O(n,p)^{17}N$	22 mb	14 MeV	4.2 s	β^-, n	
$^{16}O(n,p)^{16}N$	40 mb	14 MeV	7.4 s	β^-, γ	0.2 mg

counters, which has been developed to a patentable stage by the Weizmann Institute, allows continuous measurements on paper chromatograms[121]. However, the detection sensitivity achieved so far is only 40 to 100 µg of ^{18}O, which is unsatisfactory.

With high-energy protons, *e.g.* from the beam of a cyclotron, the heavy oxygen isotopes are converted into the positron emitters ^{18}F and ^{17}F, with simultaneous emission of neutrons. The annihilation radiation of the liberated positrons is used for the ^{18}O analysis. The resulting γ quanta are either measured directly or detected by the blackening of photographic films (autoradiography). Since a high degree of interference is caused by the ^{18}O background of natural oxygen in a paper chromatogram, the chromatograms must be eluted in segments in biochemical tracer analysis, the separated substances then being transferred to tantalum or platinum plates for the proton irradiation[122,123]. Recoil protons formed in nuclear reactors by the action of fast neutrons on substances containing water also initiate a (p,n) reaction on ^{18}O nuclei. This technique has also been used in activation analysis[124].

Amsel et al.[125,126] have developed a special irradiation and measuring apparatus for the microanalysis of oxide films on metal surfaces. This apparatus allows a parallel determination of ^{18}O by means of the (p,α) reaction and of ^{16}O by the (d,p) reaction. To measure the total quantity of an isotope in a surface segment, use is made of plateau regions of the cross-sections for the specific reactions. Thus the target is irradiated in a high vacuum with ≈700 keV protons for the ^{18}O analysis and with 800—900 keV deuterons for the ^{16}O analysis. The prompt α particles or protons are recorded. With isotope standards that can be obtained by anodic oxidation of metallic tantalum in corresponding water samples, it is possible to achieve a relative accuracy of 1% in the measurements. The detection limits is 10^{-12} g of oxygen. This technique was the precondition for the *in-vivo* isotope analysis of cell water in the brains of living rats (see Section 4.1)[90]. In addition to the pure isotope analysis, *Amsel*'s method also allows a quantitative determination of concentration profiles of the oxygen isotopes up to a layer depth of about 1 µm. The measurement of the depth distribution of oxygen is based on the resonance absorption. There is a narrow resonance at 629 keV in the cross section of the (p,α) reaction of ^{18}O (Fig. 10). If a target containing ^{18}O is bombarded with protons having exactly this resonance energy, the α particles are emitted almost exclusively from the first surface layer (50—100 Å). If the energy of the proton is increased to slightly above 629 keV, the resonance zone is displaced into the crystal lattice because of the deceleration effects. The α particles emerging

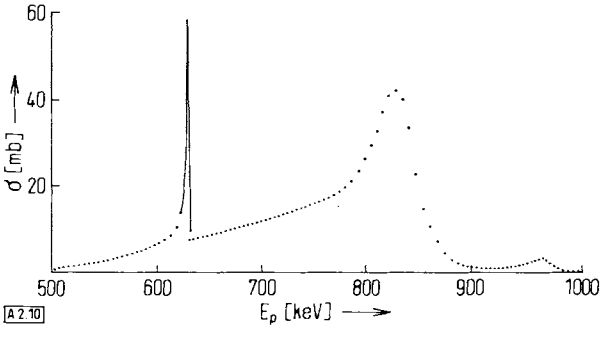


Fig. 10. Cross-section of the (p,α) reaction of the isotope ^{18}O (from *Amsel* [126]).

from the resonance zone provide a measure of the ^{18}O concentration in this zone. Figure 11 shows the ^{18}O profile in a tantalum oxide with a sandwich structure (140 Å—^{18}O/840 Å—^{16}O/420 Å—^{18}O)[126]. The Amsel method of microprofile analysis is extremely suitable for the investigation of diffusion, corrosion, and passivation phenomena in semiconductors and metals[126-128].

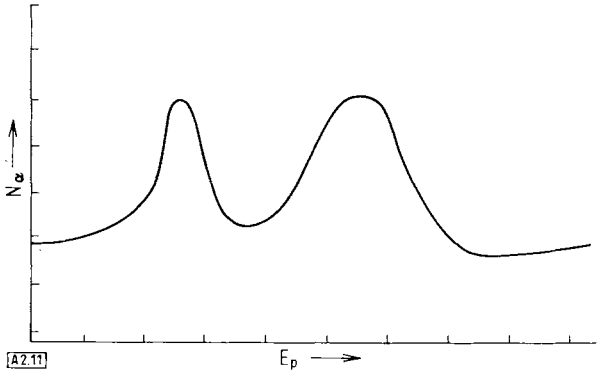


Fig. 11. Depth distribution of ^{18}O in the surface film of an electrolytically oxidized sample of tantalum with ^{18}O—^{16}O—^{18}O layering [126]. E_p = 390 eV/channel, N_α: counts/division.

Nuclear reactors moderated with light or heavy water are excellent neutron sources for activation analyses with thermal

neutrons. The ^{16}O nucleus, with its "magic" number of protons and neutrons (8), is too stable to be activated under these conditions. The ^{18}O nucleus is converted by neutron capture into the unstable ^{19}O, whose γ radiation can be used for the analysis[129]. Because of the very low cross-section, however, fairly large quantities of material are required for an analysis of this type.

The activation of ^{17}O, which has an excellent cross-section[130], seems much more promising. The ^{14}C produced here by an (n,α) reaction is also formed in the thermal neutron flux from natural ^{14}N, and is therefore not specific for the detection of ^{17}O. On the other hand, the prompt α radiation is specific for the ^{17}O process, provided that the presence of the isotopes ^{6}Li, ^{10}B, and ^{21}Ne can be ruled out. This is always so in the biological samples from tracer experiments, with the result that the (n,α) process of ^{17}O is extremely advantageous in biochemistry.

Malmon[131] suggested a microtrack method for the recording of the prompt α particles. If a chromatogram is irradiated while it is in close contact with a metal or plastic foil, the liberated α particles leave deceleration tracks in the foil; these can be counted by means of electron microscopy in gold or platinum foils or under the optical microscope in the case of plastic foils (after amplification by alkaline etching). This simple procedure on the one hand allows the simultaneous irradiation of any number of samples, and on the other it allows the localization of the tracer ^{17}O in biological fine structures. It was experimentally introduced into biochemistry by *Samuel*[90].

Activation analysis with fast neutrons responds to all three isotopes of oxygen. Fast, nondestructive analyses of many stable isotopes are possible with neutron generators that operate with accelerated deutrons and tritium targets and use the nuclear reaction

$$D + T \rightarrow {}^{4}He + n + 14\,MeV$$

for the production of 14 MeV neutrons[132]. Because of the low cross sections, the process again calls for fairly large quantities of substance in the case of the oxygen isotopes. The activation of ^{17}O leads by the reaction sequence[133]

$$^{17}O(n,p)^{17}N \xrightarrow[4.2\,s]{\beta^-} [^{17}O]^* \xrightarrow{n} {}^{16}O$$

to delayed neutrons that are easy to measure. The activation of ^{16}O with 14 MeV neutrons is a method often used for the determination of oxygen in metals, graphite, and other pure substances[134–137]. It is even applied in medicine for blood-flow measurements, in which the heart is irradiated with neutrons for one second and the 6 MeV γ radiation of the reaction product ^{16}N is then monitored in several parts of the body[138].

6.2. Radioactive Energy Sources

The development of heart pacemakers and artificial pumps, which are implanted in the human body to assist the blood circulation, has made significant progress with the use of $^{238}Pu^{16}O_2$ as an energy source. ^{238}Pu, which is produced from ^{237}Np in nuclear reactors, decomposes with a half-life of 87 years with α and γ emission[139]. A spontaneous fission with a half-life of 4.8×10^{10} years occurs at the same time. Since plutonium is used in the oxide form for reasons of chemical stability, two neutron-producing processes take place in PuO_2 containing natural oxygen, *i. e.* the spontaneous fission with a yield of about 2800 n s^{-1} g^{-1} of Pu and the (α,n) reaction of the isotopes ^{18}O and ^{17}O with a total yield of 20000 n s^{-1} g^{-1} of Pu. In addition to these there are also corresponding nuclear reactions with other trace elements, particularly fluorine[140, 141]. These processes are extremely undesirable, since the neutrons liberated pass through the wall of the power pack and activate elements in its immediate vicinity. With isotopically pure ^{16}O, at least the (α,n) process of the heavy oxygen isotopes can be completely eliminated.

Two methods are used for the preparation of $^{238}Pu^{16}O_2$. The PuO_2 obtained from Pu(III) oxalate is allowed to undergo exchange with pure $^{16}O_2$ gas at 850 to 105 °C or with $H_2{}^{16}O$ at 700 °C, and is then sintered at 1200 °C[142]. For the isotope analysis of the PuO_2, a high-temperature reduction was carried out with pure carbon, and the CO formed was determined by mass spectrometry after gas-chromatographic separation in a stream of He[143]. The best $^{238}Pu^{16}O_2$ samples obtained so far gave a neutron emission of 3000 n s^{-1} g^{-1} of Pu.

The world demand for high-purity ^{16}O for biomedical, radiation-medical, and power investigations and applications amounts to 100 to 1000 kg per year[65], and is still increasing. This fact clearly indicates that the isotopy of the material world is by no means a subject merely for investigation in fundamental research. The breakthrough in isotope research to the industrial scale, which was first achieved for deuterium, is now being paralleled by the application of the stable isotopes of the vital element oxygen.

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[1] *H. C. Urey, F. G. Brickwedde,* and *G. M. Murphy*, Phys. Rev. *40*, 1 (1932).

[2] *G. M. Murphy* in *H. Craig, S. L. Miller,* and *G. J. Wasserburg*: Isotopic and Cosmic Chemistry, North-Holland Publ. Co., Amsterdam 1964, p. 1.

[3] *D. Samuel* in *O. Hayaishi*: Oxygenases. Academic Press, New York 1962, p. 31.

[4] *D. Samuel* in *B. Hess* and *Hj. Staudinger*: 19. Colloquium der Gesellschaft für Biologische Chemie, April 1968 in Mosbach/Baden. Springer, Berlin 1968, p. 6.

[5] *A. G. Arthyukh et al.*, Phys. Lett. *B32*, 43 (1970); CERN 70-30 (Vol. 1), 47 (1970).

[6] *D. Samuel* and *F. Steckel*: Bibliography of the Stable Isotopes of Oxygen (^{17}O and ^{18}O). Pergamon Press, London 1959.

[7] *D. Samuel* and *F. Steckel*, Int. J. Appl. Radiat. Isotop. *11*, 190 (1961).

[8] *J. L. Borowitz, D. Samuel,* and *F. Steckel*, Int. J. Appl. Radiat. Isotop. *16*, 97 (1965).

[9] *D. Samuel* and *F. Steckel*, Int. J. Appl. Radiat. Isotop. *19*, 175 (1968).

[10] *F. Steckel* and *S. Szapiro*, Trans. Faraday Soc. *59*, 331 (1963).

[11] *F. Steckel* and *S. Szapiro*, Trans. Faraday Soc. *63*, 883 (1967).

[12] *R. L. Combs, J. M. Googin,* and *H. A. Smith*, J. Phys. Chem. *58*, 1000 (1954).

[13] *A. I. Kudish, D. Wolf,* and *F. Steckel*, J. C. S. Faraday Trans. I, *68*, 2041 (1972).

[14] *A. I. Kudish*, personal communication.

[15] *H. Craig*, Science *133*, 1833 (1961).

[16] *M.-T. Forel* and *M. Fouassier*, C. R. Acad. Sci. *B274*, 73 (1972).

[17] *E. Jacob* and *W. Polligkeit*, Z. Naturforsch. *28b*, 120 (1973).

[18] *E. Jacob* and *R. Opferkuch*: Chemie und Technologie des UF_6, Untersuchung der Hydrolyseprodukte des UF_6, Teil II. Darstellung und Schwin-

gungsspektren von stapelfehlerfreiem UO_2F_2 und $UO_2{}^{18}F_2$. Report KVT 69/05, Nov. 15, 1972, KFZ Karlsruhe.

[19] *E. Petreanu, S. Pinchas*, and *D. Samuel*, J. Inorg. Nucl. Chem. *27*, 2519 (1965).

[20] *S. Pinchas* and *D. Sadeh*, J. Inorg. Nucl. Chem. *30*, 1785 (1968).

[21] *S. Pinchas*, Isr. J. Chem. 7, 5 (1969); *S. Pinchas* and *J. Shamir*, *ibid.* 7, 805 (1969).

[22] *S. Pinchas*, J. Chem. Phys. *51*, 2284 (1969).

[23] *S. Pinchas, D. Samuel*, and *E. Petreanu*, J. Inorg. Nucl. Chem. *29*, 335 (1967).

[24] *S. Pinchas* and *J. Shamir*, J. Chem. Phys. *56*, 2017 (1972).

[25] *S. Pinchas*, Nature Phys. Sci. *242*, 46 (1973).

[26] *H. C. Urey*, J. Chem. Soc. *1947*, 562.

[27] *J. Bigeleisen*, J. Chem. Phys. *34*, 1485 (1961).

[28] *J. Bigeleisen*, J. Chim. Phys. Physicochim. Biol. *60*, 35 (1963).

[29] *M. Majoube*, J. Chim. Phys. Physicochim. Biol. *68*, 625 (1971).

[30] *M. Majoube*, J. Chim. Phys. Physicochim. Biol. *68*, 1423 (1971).

[31] *J. L. Borowitz* and *F. S. Klein*, J. Phys. Chem. *75*, 1815 (1971).

[32] *W. Spindel, M. J. Stern*, and *E. U. Morse*, J. Chem. Phys. *52*, 2022 (1970).

[33] *J. Bigeleisen* and *M. Wolfsberg*, Advan. Chem. Phys. *1*, 15 (1958).

[34] *A. Fry* in *C. J. Collins* and *N. S. Bowman:* Isotope Effects in Chemical Reactions. Van Nostrand-Reinhold Co., New York 1970, p. 364.

[35] *P. C. Vogel* and *M. J. Stern*, J. Chem. Phys. *54*, 779 (1971).

[36] *C. G. Mitton* and *R. L. Schowen*, Tetrahedron Lett. *1968*, 5803.

[37] *M. J. Goldstein*, Tetrahedron Lett. *1964*, 1601.

[38] *M. J. Goldstein* and *G. L. Thayer*, J. Amer. Chem. Soc. *87*, 1933 (1965).

[39] *C. R. Hart* and *A. N. Bourns*, Tetrahedron Lett. *1966*, 2995.

[40] *D. Rittenberg* in *H. Craig, S. L. Miller*, and *G. J. Wasserburg:* Isotopic and Cosmic Chemistry. North-Holland Publ. Co., Amsterdam 1964, p. 60.

[41] *R. A. Uphaus, E. Flaumenhaft*, and *J. J. Katz*, Biochim. Biophys. Acta *141*, 625 (1967).

[42] *D. Samuel, D. Wolf, A. Meshorer*, and *I. Wassermann* in *P. D. Klein* and *S. V. Peterson:* Proceedings of the First International Conference on Stable Isotopes in Chemistry, Biology and Medicine. May 1973, Argonne National Laboratory. USAEC, CONF-730525, p. 203.

[43] *P. D. Wagner, R. W. Mazzone*, and *J. B. West*, J. Appl. Physiol. *34*, 847 (1971).

[44] *A. I. Kudish, D. Wolf*, and *F. Steckel*, J. C. S. Faraday Trans. I, in press.

[45] a) *J. Bigeleisen* and *M. Wolfsberg*, J. Chem. Phys. *50*, 561 (1969); b) *W. A. Steele, ibid. 50*, 562 (1969).

[46] *B. Bonn, E. Gans, G. Sicking*, and *E. Wicke:* Diffusion Isotope Effects in Isotope Mixtures. Jul-CONF-6 (Vol. 2), 409 (1972). International Meeting on Hydrogen in Metals. Jülich, March 1972.

[47] *D. Staschewski*, Ber. Bunsenges. Phys. Chem. *69*, 426 (1965).

[48] *H. Taube*, Annu. Rev. Nucl. Sci. 6, 277 (1956).

[49] *B. Maiwald* and *K. Heinzinger*, Z. Naturforsch. *27a*, 819 (1972).

[50] *G. Dongmann, H. Förstel*, and *K. Wagener*, Nature New Biol. *240*, 127 (1972).

[51] *E. Erikson:* Isotopes in Hydrology. Proceedings of a Symposium (Vienna 1966), Held by the IAEA in Co-operation with the IUGG. Vienna 1967, p. 21.

[52] *M. Majoube* and *E. Roth:* Etude des variations des teneurs en oxygène-18 et en deuterium dans deux grelons. Note CEA-N-1540, CEN de Saclay.

[53] *H. Craig*, Science *133*, 1702 (1961).

[54] *B. R. Payne*, J. Brit. Nucl. Energy Soc. *10*, 29 (1971).

[55] *J. R. O'Neil* and *R. N. Clayton* in *H. Craig, S. L. Miller*, and *G. J. Wasserbourg:* Isotopic and Cosmic Chemistry. North-Holland Publ. Co., Amsterdam 1974, p. 157.

[56] *S. Epstein* and *T. Mayeda*, Geochim. Cosmochim. Acta *4*, 213 (1953).

[57] *C. Emiliani*, Science *154*, 851 (1966).

[58] *J. R. O'Neil* and *H. P. Taylor*, J. Geophys. Res. *74*, 6012 (1969).

[59] *R. N. Clayton*, Geochim. Cosmochim. Acta *37*, 811 (1973).

[60] *N. Onuma, R. N. Clayton*, and *T. K. Mayeda*, Geochim. Cosmochim. Acta *36*, 169 (1972).

[61] *R. N. Clayton, L. Grossman*, and *T. K. Mayeda*, Science *182*, 485 (1973).

[62] *B. M. Andrejew, T. D. Gumenjuk, J. D. Zel'venskij*, and *A. M. Mereckij:* ASTI 69, 6. Arbeitstagung über stabile Isotope, Oct. 1969 in Leipzig. Isotope Titles, Sept. 1970, Vol. 3 (Special issue), p. 250.

[63] *W. T. Boyd* and *R. R. White*, Ind. Eng. Chem. *44*, 2202 (1952).

[64] *B. B. McInteer* and *R. M. Potter*, Ind. Eng. Chem. Process Des. Develop. *4*, 35 (1965).

[65] *R. E. Schreiber:* ICONS at LASL, Report LA-4759-MS, Los Alamos, Sept. 1971.

[66] *T. I. Taylor*, J. Chim. Phys. Physicochim. Biol. *60*, 154 (1963).

[67] *I. G. Gverdtziteli et al.*, 3rd Geneva Conferenz, A/CONF. 28/P/388, USSR, May 1964.

[68] *H. London:* Proceedings of the International Symposium on Isotope Separation 1957. North-Holland Publ. Co., Amsterdam 1958, p. 319.

[69] *E. Krell*, Chem. Ing. Tech. *32*, 233 (1960).

[70] *D. Wolf* and *H. Cohen*, Can. J. Chem. Eng. *50*, 621 (1972).

[71] *Z. Fraenkel, A. Raviv*, and *W. Klein*, Chem. Eng. Sci. *18*, 697 (1963).

[72] *J. S. Drury et al.*, Report ORNL-3832, Sept. 1965; ORNL-TM 1047 (1965); ORNL-3994, Jan. 1967, p. 27.

[73] *D. Staschewski*, Chem. Ing. Tech. *43*, 810 (1971).

[74] *D. Staschewski:* Proceedings of the International Meeting on Isotope Effects in Physical and Chemical Processes. June 1973, Cluj (Romania).

[75] *G. Kretzschmann:* ASTI 69, 6. Arbeitstagung über stabile Isotope, Oct. 1969 in Leipzig. Isotope Titles, Sept. 1970, Vol. 1 (Special issue), p. 1.

[76] *M. Polanyi* and *A. L. Szabo*, Trans. Faraday Soc. *30*, 508 (1934).

[77] *J. H. Espenson* and *H. Taube*, Inorg. Chem. *4*, 704 (1965).

[78] *R. Buchacek* and *G. Gordon*, Inorg. Chem. *11*, 2154 (1972).

[79] *M. Lacroix*, Bull. Soc. Roy. Sci. Liege *40*, No. 3 -4, 179 (1971).

[80] *D. Staschewski*, Chem.-Ztg. *98*, 77 (1974).

[81] *H. Mason, W. L. Fowlks*, and *E. Peterson*, J. Amer. Chem. Soc. *77*, 2914 (1955).

[82] *O. Hayaishi, M. Katagiri*, and *S. Rothberg*, J. Amer. Chem. Soc. *77*, 5450 (1955).

[83] *S. Ruben, M. Randall, M. Kamen*, and *J. W. Hyde*, J. Amer. Chem. Soc. *63*, 877 (1941).

[84] *D. Staschewski:* Photosynthese und Sauerstoffaustausch bei Grün- und Blaualgen nach ^{18}O-Markierungsversuchen mit strömendem Kohlendioxid-Gas. Report KFK-1137, Feb. 1970, KFZ Karlsruhe.

[85] *H. Metzner*, J. Theor. Biol., in press.

[86] *V. S. Saakov:* ASTI 69, 6. Arbeitstagung über stabile Isotope, Oct. 1969 in Leipzig. Isotope Titles, Sept. 1970, Vol. 3 (Special issue), p. 195.

[87] *R. J. Volk* and *W. A. Jackson*, Plant Physiol. *49*, 218 (1972).

[88] *H. R. Gutmann* and *R. R. Erickson*, J. Biol. Chem. *247*, 660 (1972).

[89] *D. Samuel*, Naturwiss. Rundsch. *23*, 458 (1970).

[90] *D. Samuel* in *P. D. Klein* and *S. V. Peterson:* Proceedings of the First International Conference on Stable Isotopes in Chemistry, Biology and Medicine. May 1973, Argonne National Laboratory. USAEC, CONF-730525, p. 196.

[91] *B. Z. Shakhashiri* and *G. Gordon*, J. Inorg. Nucl. Chem. *28*, 2525 (1966).

[92] *E. R. Winter*, J. Chem. Soc. *A 1968*, 2889.

[93] *J. Novakova*, Catal. Rev. *4*, 77 (1970).

[94] *B. Cox* and *J. P. Pemsler*, J. Nucl. Mater. *28*, 73 (1968).

[95] *J. B. Holt* and *L. Himmel*, J. Electrochem. Soc. *116*, 1569 (1969).

[96] *P. Contamin, J. J. Bacmann*, and *J. F. Marin*, J. Nucl. Mater. *42*, 54 (1972).

[97] *D. Samuel* and *B. L. Silver*, Advan. Phys. Org. Chem. *3*, 123 (1965).

[98] *K. Uchida* and *K. Aida*, Biochem. Biophys. Res. Commun. *46*, 130 (1972).

[99] *D. Staschewski*, Chem. Ing. Tech. *41*, 1111 (1969).

[100] *R. Gerster*, Int. J. Appl. Radiat. Isotop. *22*, 339 (1971).

[101] *R. H. Gerster, T. H. Maren*, and *D. N. Silverman* in *P. D. Klein* and *S. V. Peterson:* Proceedings of the First International Conference on Stable Isotopes in Chemistry, Biology and Medicine. May 1973, Argonne National Laboratory. USAEC, CONF-730525, p. 219.

[102] *D. Silverman*: Proceedings of the First International Conference on Stable Isotopes in Chemistry, Biology and Medicine. May 1973, Argonne National Laboratory. USAEC, CONF-730525, p. 239.

[103] *H. Gamsjäger, A. Grütter*, and *P. Baertschi*, Helv. Chim. Acta *55*, 781 (1972).

[104] *H. Gamsjäger* and *P. Baertschi*, Helv. Chim. Acta *55*, 2154 (1972).

[105] *N. C. Yang, W. Eisenhardt*, and *J. Libman*, J. Amer. Chem. Soc. *94*, 4030 (1972).

[106] *H. Tamada* and *K. Furuya*, Bull. Chem. Soc. Jap. *41*, 1256 (1968).

[107] *B. L. Silver* and *Z. Luz*, Quart. Rev. Chem. Soc. *21*, 458 (1967).

[108] *Z. Luz* and *G. Yagil*, J. Phys. Chem. *70*, 554 (1966).

[109] *P. Greenzaid, Z. Luz*, and *D. Samuel*, Trans. Faraday Soc. *64*, 2780 (1968).

[110] *P. Greenzaid, Z. Luz*, and *D. Samuel*, Trans. Faraday Soc. *64*, 2787 (1968).

[111] *P. Diehl, H. A. Christ*, and *F. B. Mallory*, Helv. Chim. Acta *45*, 504 (1962).

[112] *A. J. Tench*, J. C. S. Faraday Trans. I, *68*, 1181 (1972).

[113] *A. J. Tench, T. Lawson*, and *J. F. J. Kibblewhite*, J. C. S. Faraday Trans. I, *68*, 1169 (1972).

[114] *A. J. Tench* and *P. Holroyd*, Chem. Commun. *1968*, 471.

[115] *A. I. Schatenstein*: Isotopenanalyse des Wassers. VEB Deutscher Verlag der Wissenschaften, Berlin 1960.

[116] *D. Staschewski*, Ber. Bunsenges. Phys. Chem. *73*, 59 (1969).

[117] *D. Rittenberg* and *L. Ponticorvo*, Int. J. Appl. Radiat. Isotop. *1*, 208 (1956).

[118] *M. Anbar* and *S. Guttmann*, Int. J. Appl. Radiat. Isotop. *5*, 233 (1959).

[119] *G. W. Leddicotte* in *D. Glick*: Methods of Biochemical Analysis. Vol. 19, Interscience, New York 1971, p. 345.

[120] *J.-P. Adloff, J.-J. Schleiffer*, and *C. Urlacher*, Bull. Soc. Chim. Fr. *1966*, 698.

[121] *S. Amiel* and *A. Nir*: Proceedings of the Symposium on Radiochemical Methods of Analysis. Salzburg 1974, I, p. 287.

[122] *I. Fogelström-Fineman, O. Holm-Hansen, B. M. Tolbert*, and *M. Calvin*, Int. J. Appl. Radiat. Isotop. *2*, 280 (1957).

[123] *A. Fleckenstein, E. Gerlach, J. Janke*, and *P. Marmier*, Naturwissenschaften *46*, 365 (1959).

[124] *D. C. Aumann* and *H. J. Born*, Naturwissenschaften *51*, 199 (1964).

[125] *G. Amsel* and *D. Samuel*, Anal. Chem. *39*, 1689 (1967).

[126] *G. Amsel, J. P. Nadai, E. D'Artemare, D. David, E. Girard*, and *J. Moulin*, Nucl. Intrum. Methods *92*, 481 (1971).

[127] *J. Siejka, C. Cherki*, and *J. Yahalom*, Electrochim. Acta *17*, 161 (1972).

[128] *C. Herold, P. Schubert*, and *W.-D. Schulz*, Isotopenpraxis *8*, 321 (1972).

[129] *Y. Kamemoto*, Nature *203*, 513 (1964).

[130] *G. C. Hanna, D. B. Primeau*, and *P. R. Tunnicliffe*, Can. J. Phys. *39*, 1784 (1961).

[131] *A. G. Malmon*, J. Theor. Biol. *9*, 77 (1965).

[132] *F. Lux*: Forschungs- und Entwicklungsprogramm für die Aktivierungsanalyse in der Bundesrepublik Deutschland. BMFT-FB/K 73-27, Sept. 1973.

[133] *H. O. Menlove, R. H. Augustson*, and *C. N. Henry*, Nucl. Sci. Eng. *40*, 136 (1970).

[134] *M. Schmidt-Hönow* and *W. Herr*, Chem. Ing. Tech. *40*, 1182 (1968).

[135] *A. Barwinski et al.*, Isotopenpraxis *4*, 15 (1968).

[136] *D. Brune* and *K. Jirlow*, J. Radioanal. Chem. *2*, 49 (1969).

[137] *R. Neider, B. F. Schmitt, P. Reimers*, and *P. Mlitz*, Materialprüfung *11*, 28 (1969).

[138] *M. Auphan, J. Perilhou*, and *H. Spaa*, C. R. Acad. Sci. *D 273*, 1995 (1971).

[139] *T. K. Keenan, R. E. Vallee*, and *J. A. Powers*: Radiation from Pu^{238} Used in Space Application. NASA-TM-X-2440, Jan. 1972, p. 859.

[140] *R. A. Neff, M. E. Anderson, A. R. Campbell*, and *F. X. Haas*: Some Neutron and γ Radiation Characteristics of Plutonium Cermet Fuel for Isotopic Power Sources. NASA-TM-X-2440, Jan. 1972, p. 853.

[141] *V. A. Arkhipov et al.*, Sov. At. Energy *32*, 347 (1972) (Transl. of At. Energ., p. 310).

[142] *J. C. Miles, R. L. Deaton*, and *C. J. Wiedenheft*: Oxygen Isotope Exchange of $P^{238}O_2$. MLM-1891, Feb. 1972.

[143] *C. S. MacDougall, M. E. Smith*, and *G. R. Waterbury*: Determination of $^{18}O/^{16}O$ Atom Ratio in Plutonium Dioxid Enriched in ^{16}O. LA-4849, Feb. 1972.

Photochemistry in Interstellar Space and Reactions Generating Interstellar Molecules

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Over 20 different molecules and radicals have so far been detected in interstellar space. The number of such molecules and radicals and their frequently complicated structure raise the question of the processes leading to their formation. Diatomic molecules and radicals could arise in gas-phase reactions. Formation of polyatomic molecules can be explained in terms of reactions proceeding on the surface of dust particles and possibly involving interstellar radiation. The author demonstrates, with the aid of a model, that the molecular abundances and distributions within dust clouds in certain regions can be explained by photocatalytic reactions.

1. The Interstellar Medium

The discovery of over 20 molecules (including polyatomic radicals) in interstellar space by radioastronomy has opened up a new area of study uniting two fundamentally different branches of research, astrophysics and chemistry. To the astrophysicist the molecules are excellent probes for research into the interstellar medium since their spectra yield information about the physical conditions at the location of the molecule which is inaccessible to all other observational techniques applied today. For the chemist the question arises how molecules are formed at all in interstellar space. Any answer to this question requires that we first characterize interstellar space and the interstellar medium and examine what factors can affect the formation and dissociation of molecules.

Interstellar space is occupied by material composed mainly of two components, interstellar gas and interstellar dust. The chemical composition of interstellar gas follows from the relative cosmic abundances of the elements (Table 1). Hydrogen, responsible for 70% by mass, is the most common element, followed by helium (28%). Elements heavier than helium constitute the remaining 2%.

All available evidence indicates that this composition is constant throughout our galactic system. Interstellar dust is amenable to observation only where its density is sufficiently great. The negative photograph of the Orion nebula reproduced in Figure 1 illustrates a concentration of this kind.

The areas appearing dark are regions of intense optical radiation arising from the ionized gaseous component. The contours

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Table 1. Relative cosmic abundance of the elements (after [1]).

Element	Abundance relative to H	First ionization potential [eV]
H	1.0	13.6
He	1.0×10^{-1}	24.6
C	2.3×10^{-4}	11.3
N	1.3×10^{-4}	14.5
O	6.0×10^{-4}	13.6
Ne	2.0×10^{-4}	21.6
Na	4.4×10^{-6}	5.1
Mg	4.4×10^{-5}	7.6
Al	2.2×10^{-6}	6.0
Si	4.8×10^{-5}	8.1
S	2.1×10^{-5}	10.4
Ar	7.1×10^{-6}	15.8
Ca	2.5×10^{-6}	6.1
Fe	3.2×10^{-5}	7.9

shown link points of equal radio emission. Towards the center of the radio frequency emission, the optical radiation appears to be blocked over a wide streak, appearing white in the Figure, while the radio frequency emission remains unaffected. This blocking of the optical radiation is due to interstellar dust. The diameter of the dust particles is of the same order of magnitude as the wavelength of optical radiation: hence the latter is strongly attenuated. In contrast, the dust particles have little influence on the longer radio waves.

Whereas extinction and polarization measurements provide comparatively reliable information about the size of the dust particles, only very little is known about their chemical composition. The range of materials suggested extends from ice *via* metals to diamond. However, recent observations[2] suggest that at least some of the regions contain silicates. The Orion nebula is just one example of a cloud made up of gas and dust. Observations show that a whole range of cloud types exist. They differ primarily with regard to density, *i.e.* the concentration of dust, and size[*]. In the extreme case, gravitational forces can arise in very dense clouds which can overcome the internal gas pressure. The cloud then collapses to form the precursor of a new star.

Since the interstellar molecules are observed mainly in dust clouds, and these optically dense clouds are accessible to radioastronomical measurements, it becomes possible to directly observe star formation at this stage.

In the various types of clouds the hydrogen density[**], and thus also the density of the other elements, varies between 10 and $10^7\,cm^{-3}$. The ratio of hydrogen density to the dust density is about 10^{10}. The kinetic gas temperatures are likewise dependent upon the density. Outside the cloud several 10^3 °K are observed at a hydrogen density of $1\,cm^{-3}$ while this temperature can drop to well below 100 °K in dense clouds.

The temperature of the dust particles, which absorb energy in the visible and ultraviolet and radiate in the far infrared, lies between 50 and 20 °K, depending on size and chemical composition, in free interstellar space. In very dense clouds the temperature can be as low as 5 °K.

Further characterization of the interstellar medium also includes the interstellar radiation field, the integrated radiation emitted by the stars into interstellar space. However, only the spectral range above 912Å is of interest since photons having $\lambda \leqslant 912$ Å are able to ionize hydrogen and are therefore absorbed in the immediate vicinity of the emitting star. According to *Habing*[3] the radiation density in dust-free regions has a mean value of $U_\lambda = 4 \times 10^{-17}\,erg\,Å^{-1}\,cm^{-3}$[***]. The

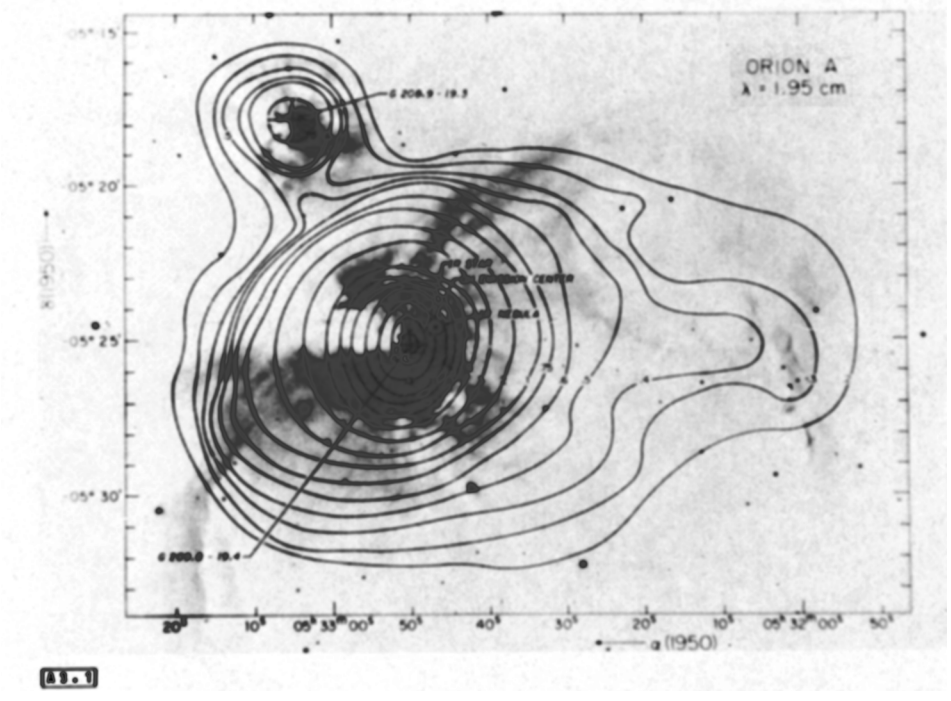


Fig. 1. Negative reproduction of the Orion nebula. Explanations in text. The Orion nebula is situated about 1.6×10^3 light years from the Earth. The photograph was kindly provided by the Max-Planck-Institut für Radioastronomie, Bonn.

[*] The radii of the clouds are in the range 10^{18}—10^{20} cm.

[**] The hydrogen density is defined as $N_H\,cm^{-3}$.

[***] Recent satellite measurements [4] show that the radiation flux rises to about 10×10^{-17} erg Å cm^{-3} in the proximity of the sun.

wavelength-dependent extinction of the radiation by interstellar dust is shown in Figure 2.

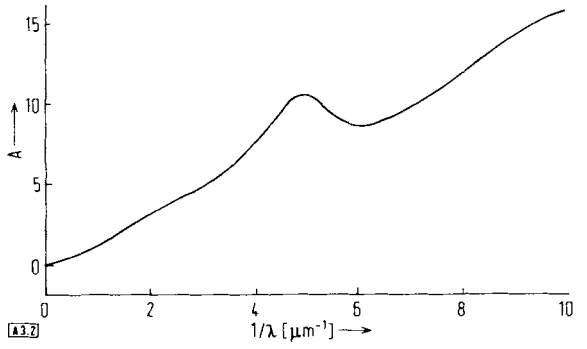


Fig. 2. Extinction A of interstellar radiation by dust as a function of the wavelength (after [1]). The extinction is proportional to the optical depth. $1/\lambda = 2\,\mu m^{-1}$ corresponds to $\lambda = 5000$ Å, $1/\lambda = 10\,\mu m^{-1}$ corresponds to $\lambda = 1000$ Å.

For our further treatment of molecule formation and the lifetimes of interstellar molecules it is of importance that the extinction increases very steeply with decreasing wavelength.

2. Interstellar Molecules

2.1. Interstellar Molecules and Theoretical Models of Molecule Formation

The molecules identified so far in interstellar space are listed in Table 2. Three representatives, namely CN, CH, and CH^+, were detected as long ago as 1940 by their optical spectra[5]. However, the majority of these molecules were found by radioastronomic measurements, generally by observing rotational transitions in the electronic ground state.

Table 2. List of molecules and radicals discovered in interstellar space (after [1]).

Molecule	Spectral region	Column density [cm^{-2}] [a]	Year of discovery
H_2	UV	$\approx 10^{20}$	1970
OH	cm	10^{12}—10^{16}	1963
SiO	mm	$\approx 10^{13}$	1971
H_2O	cm	?	1969
NH_3	cm	?	1968
CH	visible	$\approx 10^{13}$	1937
CH^+	visible	$\approx 10^{13}$	1941
CN	mm, visible	$\approx 10^{15}$	1940
CO	mm, UV	10^{17}—10^{19}	1970
CS	mm	10^{13}—10^{14}	1971
OCS	mm	$\approx 10^{16}$	1971
HCN	mm	10^{14}—10^{15}	1970
H_2CO	cm	10^{12}—10^{16}	1969
HNCO	cm, mm	$\approx 10^{14}$	1971
H_2CS	cm	?	1971
HCOOH	cm	$< 10^{13}$	1970
HC_3N	cm, mm	$\approx 10^{16}$	1970
H_2CNH	cm	$\approx 10^{14}$	1972
CH_3OH	cm, mm	?	1970
CH_3CN	mm	$\approx 10^{14}$	1971
$HCONH_2$	cm	$> 10^{11}$	1971
$HCOCH_3$	cm	$\approx 10^{14}$	1971
CH_3CCH	mm	?	1971

[a] The column density is defined as the volume density integrated over the visual beam and projected onto $1\,cm^2$. The densities given here are mean values.

As more and more interstellar molecules were discovered, increasing attention was focused on the question of possible formation reactions. In view of the varying conditions of density and temperature in interstellar space it would appear unlikely that all the molecules observed are formed by the same type of reactions. For instance, formation of diatomic molecules and radicals can be explained by binary collisions in the gas phase. *Solomon* and *Klemperer*[6] have calculated the densities of diatomic molecules for a particular region of the constellation Ophiuchus for which adequate observational data are available[7]. Assuming a kinetic gas temperature of 20 °K, a hydrogen density of $100\,cm^{-3}$, and the corresponding relative densities of other elements according to Table 1, about 30 simultaneous exothermic reactions were considered.

The most important reaction was found to be

$$C^{\oplus} + H \rightarrow CH^{\oplus} + h\nu$$

The reaction

$$C + H \rightarrow CH + h\nu$$

is of less significance since under the prevailing conditions the interstellar radiation is able to almost completely ionize atomic carbon. The other diatomic molecules and radicals are formed in exchange reactions. Some densities calculated in this way are compared with observed values in Table 3.

Table 3. Comparison of calculated and observed column densities of diatomic molecules and radicals (after [6]).

	Column density [cm^{-2}] obs.	calc.
CH	4.3×10^{13}	1.7×10^{13}
CH^+	2.6×10^{13}	1.3×10^{13}
CN	8.3×10^{12}	6×10^{12}
NH	$< 8 \times 10^{12}$	0
OH	$< 7 \times 10^{13}$	0
CO	—	2.4×10^{14}
$C_2 + C_2^+$	—	7×10^{12}

The discrepancies, which are sometimes of considerable size, arise on the one hand from the lack of precise knowledge of some of the transition probabilities required in calculation of the rate constants, and on the other from the considerable errors that can occur in the column densities determined from radioastronomical observations.

Much greater difficulties are associated with the question of formation of polyatomic molecules. In principle, the presence of the molecules can be explained in two ways: The saturated molecules could have been formed by successive addition of atoms or radicals; alternatively, the observed molecules may have been formed from fragments of larger molecules originating from comets[8] or produced in regions of very high density and temperature[9], for example where a new star is formed, and transported by radiation pressure to the cold clouds. For reasons discussed in Section 2.3, the second explanation is highly improbable.

Dalgarno and *McRay*[10] studied the gas-phase formation of molecules in reactions involving negative ions. Their results show that the rates of formation of OH and H_2O are suffi-

ciently large in clouds of low density. H_2CO can be formed by reactions involving $H^{\ominus}$ or $O^{\ominus}$ according to:

$$H^{\ominus} + HCO \rightarrow H_2CO + e^{\ominus}$$
$$O^{\ominus} + CH_2 \rightarrow H_2CO + e^{\ominus}$$

However, the rates of formation are too small to provide the sole explanation of the observed abundances. Application of this reaction mechanism to more dense clouds assumes the presence of an ionizing radiation source within, or in the close proximity of, the cloud.

For energetic reasons, many of the observed molecules can only be formed by three-body collisions in the gas phase. However, owing to the low densities encountered in interstellar space the probability of three-body collisions is much too low to account for the molecular densities observed. Interstellar dust is therefore now thought to play an essential role in the formation of polyatomic molecules. Since, as already mentioned, the chemical composition of the dust particles is unknown, nothing can be said about their catalytic activity. Merely assuming that atoms or relatively small radicals are adsorbed onto the surface of dust particles, it can be shown that the residence times for all pertinent atoms and radicals are of adequate duration and that, in spite of the low environmental temperatures, the atoms are capable of diffusing over the surface and of undergoing mutual interaction.

Possible reactions of this kind have been examined by *Watson* and *Salpeter* in a theoretical study[11]. Although their investigation indicated adequately fast rates of formation on the surface of dust particles, the proposed model requires photons in the wavelength range between 1000 and 2000 Å for the desorption process. However, this part of the radiation field will experience pronounced attenuation in the more dense clouds in which most of the molecules are observed (see Fig. 2).

2.2. Experimental Studies on Molecule Formation in Surface Reactions

Various experimental studies have indicated that radiation above 2000 Å can have some influence on molecule formation.

In simulation experiments on the formation of organic molecules on the surface of Mars, *Hubbard et al.*[12] obtained $^{14}CO_2$, ^{14}C-formaldehyde, and ^{14}C-acetaldehyde, as well as several other organic compounds containing ^{14}C which could not be uniquely identified. The starting materials were ^{14}CO and water vapor, diluted in $^{12}CO_2$ or nitrogen. Either sterilized and baked soil or ground Vycor glass was employed as substrate. The wavelength region of the radiation used was between 2000 and 3000 Å.

Similar results were previously obtained by *Breuer* and *Moesta*[13] on irradiation of gases adsorbed onto metal surfaces. In these experiments, gases such as hydrogen, nitrogen, oxygen, carbon monoxide, and methane were adsorbed onto ultrapure metal surfaces (tungsten and nickel) under ultrahigh vacuum conditions and irradiated with 2537-Å light (mercury resonance line). It had been established in earlier work[13a] that photoreactions are possible in adsorbed layers in this wavelength range. The gases were chosen so as to include the most common elements found in interstellar gas and to ensure that small molecules, such as CO and hydrocarbon radicals, are present in the adsorbed layer. While the metals used on no account reflect the physical and chemical composition of interstellar dust, they do have the advantage of permitting work on well defined surfaces and the study of the true primary steps of the photoreactions without fear of spurious results due to interfering impurities. The reaction products were detected by mass spectrometry. Moreover, deuterated gases (D_2, CD_4) were used and the natural isotopic abundances $^{12}C/^{13}C$ were observed to guarantee correct identification. The initial reaction consists in electronic excitation of the adsorbed CO molecules, followed by dissociation into C and O atoms. The C and O atoms which may be excited can react further with other adsorbed atoms, molecules, or radicals.

Table 4 lists the molecules identified in the experiments. Owing to the method of detection employed, no final decision can be reached whether the radicals observed are fragmentation products formed in the ion source of the mass spectrometer or whether they are desorbed as radicals from the surface. For some of the molecules, the cross-sections for formation and desorption from the surface are also given. These cross-sections can be calculated from the spatial requirement of the molecules, the quantum yield of the corresponding photoreaction, and from apparatus parameters such as pumping rate, radiant flux, *etc.*

Table 4. Identified radicals and molecules as products of photocatalytic reactions. Substrate: tungsten; $\lambda = 2537$ Å.

Adsorbed gases	Identified products	Cross-section [cm^2]
CO	C_2O, CO_2, C_2O_2, C_3O_2	
CO, CH_4	H_2CO	10^{-16}
CO, H_2, N_2	CN	1.5×10^{-18}
	HCN	5×10^{-19}
	N_2H	
	NO	
	N_2H_2	
	C_2N	
	C_2HN	
	C_2H_2N	
	CH_3CN	1.5×10^{-18}
	HNCO	1×10^{-18}
	N_2O	
	$HCONH_2$	1×10^{-18}
	HC_3N	5×10^{-19}

The order of magnitude of the cross-sections shows that these photoreactions can make a considerable contribution to the production of molecules. It should, however, be borne in mind when applying these results to molecule formation in interstellar space that the desorption probability may be reduced by the low environmental temperature[*], and that the catalytic activity of the dust particles and their surface heterogeneity are unknown.

2.3. Lifetimes of Interstellar Molecules

Whereas considerable uncertainty still surrounds the events occurring in molecule formation, more precise information

[*] Recent experiments have shown that the formation reaction also proceeds at 65 K.

is available about their dissociation, and hence about their lifetimes. *Stief*[14] estimated the lifetimes in clouds of various dust concentrations. The lifetime of a molecule against photodissociation depends upon three factors: the absorption cross-section; the quantum yield; and the radiation field to which the molecule is exposed.

Apart from the "interstellar" molecules CO, H_2O, H_2CO, OCS, and NH_3, the calculations included a number of others whose existence is suspected but not yet confirmed.

In the wavelength region above 912Å the quantum yield Φ for dissociation is about unity for all molecules except CO; this molecule has the highest dissociation energy (11.1 eV ≙ 1115 Å). At higher densities, dissociation can also occur at wavelengths above 1115 Å. However, since dissociation then involves collisions with excited molecules this event is negligible under interstellar conditions. No laboratory studies have been performed in the wavelength range between 1115 and 912 Å so that no adequate answer can be given regarding the dissociation probability of CO in interstellar space.

Stief's calculations show that in dust-free regions the lifetimes of all the molecules studied are less than 100 years. In Figure 3 the lifetimes of several molecules are plotted as functions of the extinction in the cloud, and thus as functions of the dust concentration.

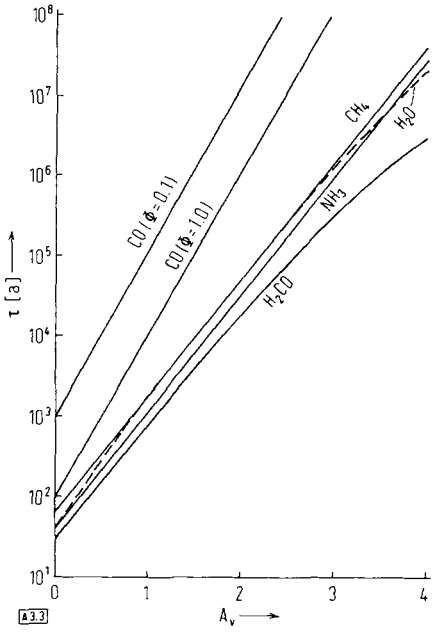


Fig. 3. Calculated lifetimes τ of several molecules as a function of the dust density, expressed as the extinction in the visible region, A_v; Φ = quantum yield (after *Stief* [14]).

Owing to the uncertainty associated with determination of the dissociation quantum yield for carbon monoxide the lifetime is calculated for two different values (Φ = 0.1; Φ = 1.0). The fact that the lifetimes in dust free regions are below 100 years has a direct consequence in molecule formation. In this very short time (on an astronomical scale), the molecules can only travel a distance which is much shorter than that between two clouds. Hence it follows that molecules can only be formed in those clouds in which they are observed. The possibility that the molecules were formed in other regions, mentioned in Section 2.1, is therefore ruled out.

3. Model for Formation and Distribution of Molecules in Dust Clouds

The unknown chemical and physical properties of the dust particles clearly complicate any discussion of concepts pertaining to molecule formation. Lack of precise knowledge of the chemical nature of the adsorption layer presents a further difficulty. Assuming that the original coverage reflects the cosmic abundances of the elements, the composition can change unpredictably as soon as a reaction starts and radicals appear on the surface. If the dust particles also have catalytic properties, certain reactions may proceed preferentially and the composition of the adsorption layer undergoes drastic changes.

However, in order to estimate whether photocatalytic reactions can contribute to molecular densities as observed in interstellar space, in spite of the difficulties mentioned, one can make the following assumption[15]: The surface of the dust particles is completely occupied by "reactive particles". A photon flux which can be calculated from the radiation density impinges on the surface. Compared with the radiation outside the cloud, the photon flux is attenuated by a factor of 10^3 by the dust. This attenuation corresponds to a dust density of 10^{-10} cm^{-3}. The dust particles have a diameter of 0.1 μm. An average value of 10^{-18} cm^2 is adopted for the cross-section for formation and desorption. At an attenuation of 10^3, the mean lifetime τ is about 10^{13} s[13].

For $\approx 10^{15}$ adsorbed particles per cm^2 dust surface and a photon flux (in the range 2000 to 3000 Å) of 1.5×10^5 cm^{-2} s^{-1} we thus obtain a mean steady-state molecular density of about 5×10^{-5} cm^{-3}, or, for a cloud diameter of 10^{19} cm (*ca.* 10 light years), a column density of 5×10^{14} cm^{-2}. Comparison with Table 2 shows that this value roughly corresponds to the mean molecular density of the polyatomic molecules.

Since formation of molecules in photocatalytic reactions occurs at higher wavelengths than photodissociation in the gas phase, the distribution of the molecules in dust clouds can be qualitatively pictured as shown in Figure 4.

A Gaussian distribution is assumed for the dust cloud; however, the same considerations apply to other distributions. Division of the radiation density into $U_\lambda < 2000$ Å and $U_\lambda > 2000$ Å accounts for the fact that the short-wave ultraviolet radiation is much more strongly attenuated than the longer wavelength component. Since molecule formation is directly proportional to the dust density, the greatest molecular densities are expected at the center of the cloud, or at the point of highest dust concentration for irregular dust distributions. This case is shown for the molecules M_1 and M_2.

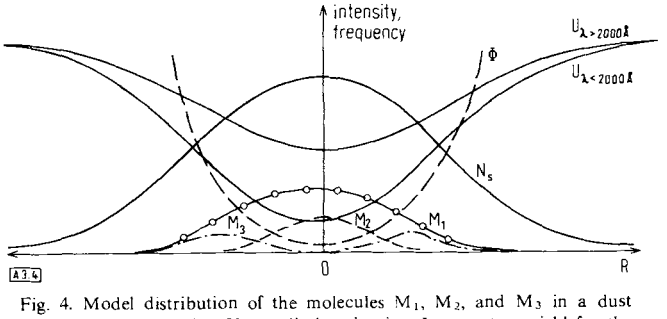


Fig. 4. Model distribution of the molecules M_1, M_2, and M_3 in a dust cloud. N_s = dust density, U_λ = radiation density, Φ = quantum yield for the photodissociation, R = distance from center of cloud.

If $\sigma_1 > \sigma_2$ (formation cross-section for molecules M_1 and M_2, respectively) a greater abundance will result for M_1 than for M_2 for the same wavelength dependence. Should higher photon energies be required for a formation reaction, the maximum shifts to a region into which the corresponding radiation penetrates with sufficient intensity. Owing to the lower dust concentrations and the enhanced dissociation probability, correspondingly reduced molecular densities will then be expected. M_3 reflects this kind of behavior. The size of the molecular clouds is limited by the photodissociation, which, in turn, is a function of the dust density. The curve designated Φ in Figure 4 is the integral quantum yield, which reaches the value 1 in dust-free regions.

Distributions of this kind, where several kinds of molecules are mixed in the interior of the cloud while the individual molecular species occupy regions of differing size, are indeed observed.

4. Summary and Outlook

It is now regarded as certain that polyatomic interstellar molecules are formed on the surface of dust particles. However, uncertainty still surrounds the question of which reactions are responsible for their formation. An attempt has been made in the above model to show that an effective contribution of photocatalytic reactions can be deduced from experimental results such as cross-sections, or from astronomic observations such as radiation densities and dust particle sizes.

Laboratory experiments have shown that many other molecules and radicals are formed in addition to the molecules observed in interstellar space. Thus molecules such as C_2H_2, CH_4, or CO_2, whose detection by radioastronomic methods is extremely difficult if at all possible, are also presumed to occur in interstellar space. Any overall picture of chemical reactions in interstellar space should, of course, also include these molecules. For the same reason, a structural selection, such as could be read off from Table 2, would appear purely accidental.

A deeper understanding of the physical and chemical conditions in interstellar space will require both further extensive radioastronomic studies and laboratory experiments. The latter could represent a valuable supplement to radioastronomical observations, since simulation experiments could, for example, elucidate the chemical structure of interstellar dust or answer the question why NO is not observed as an interstellar molecule.

5. Addendum[*]

Since the observation and study of interstellar molecules is a very young branch of scientific research, it is hardly surprising that a large number of publications in this field have appeared since the completion of this manuscript in May 1973. Two of these papers should not go without mention here. In a review article *McNally*[16] has described the formation and destruction mechanisms currently under discussion. A special model for very dense dust clouds is discussed by *Herbst* and *Klemperer*[17]. In these very dense clouds the hydrogen is present exclusively in molecular form. The density is given as $10^4 cm^{-3} < N_{H_2} < 10^6 cm^{-3}$. Since optical radiation can only penetrate the outermost layers at these densities, cosmic radiation in the 100 MeV range is considered as energy source. In all, about 100 homogeneous gas phase reactions are investigated which explain the formation of molecules such as H_2O, HCN, NH_3, and H_2CO by various routes. The model also permits an estimate of the time required until a steady state is reached for the various molecules. Dust plays an important role in this model because molecular hydrogen participates in the primary step of these reactions. However, the formation of molecular hydrogen can only be explained by means of a surface reaction.

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[1] *G. Winnewisser, P. G. Mezger*, and *H. D. Breuer*: Topics in Current Chemistry, Vol. 44: Cosmochemistry. Springer, Berlin, 1973.

[2] *N. J. Woolf*, Proc. IAU Symp. No. 52, Albany, N. Y. 1972, in press.

[3] *H. J. Habing*, Bull. Astron. Inst. Neth. *19*, 421 (1968).

[4] *A. N. Witt*, Proc. IAU Symp. No. 52, Albany, N. Y. 1972, in press.

[5] *W. S. Adams*, Astrophys. J. *93*, 11 (1941).

[6] *P. M. Solomon* and *W. Klemperer*, Astrophys. J. *178*, 389 (1971).

[7] *G. H. Herbig*, Z. Astrophys. *68*, 243 (1968).

[8] *C. Sagan*, Nature *238*, 77 (1972).

[9] *E. Anders*, Proc. Symp. Interstellar Molecules, Charlottesville, Va. 1971, in press.

[10] *A. Dalgarno* and *R. A. McRay*, Astrophys. J. *181*, 95 (1973).

[11] *W. D. Watson* and *E. E. Salpeter*, Astrophys. J. *174*, 321 (1972).

[12] *J. S. Hubbard, J. P. Hardy*, and *N. H. Horowitz*, Proc. Nat. Acad. Sci. USA *68*, 574 (1971).

[13] a) *H. Moesta* and *H. D. Breuer*, Naturwissenschaften *57*, 38 (1970); b) *H. D. Breuer, H. Moesta*, and *N. Trappen*, *ibid.* *57*, 452, 453 (1970).

[14] *L. J. Stief*, Mol. Photochem. *4*, 152 (1972).

[15] *H. D. Breuer* and *H. Moesta* in *C. de Jager*: Highlights of Astronomy. D. Reidel, Dordrecht 1971, p. 432; *H. D. Breuer*, Proc. Symp. Interstellar Molecules. Charlottesville, Va. 1971, in press; Habilitationsschrift, Universität Saarbrücken 1971; Proc. IAU Symp. No. 52. Albany, N. Y. 1972, in press.

[16] *D. McNally*, Advan. At. Mol. Phys. *8*, 1 (1972).

[17] *E. Herbst* and *W. Klemperer*, Astrophys. J. *185*, 505 (1973).

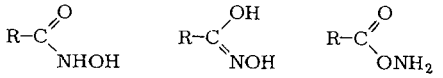
The Chemistry of Hydroxamic Acids and *N*-Hydroxyimides

By Ludwig Bauer and Otto Exner[*]

This progress report is concerned primarily with problems relating to the structure and reactions of hydroxamic acids and *N*-hydroxyimides, and also surveys some of the biological activities of these compounds. Particular significance attaches to the Lossen rearrangement of *O*-acylated hydroxamic acids, which leads to isocyanates or their reaction products.

1. Introduction

The chemistry of hydroxamic acids began in 1869 when *H. Lossen*, working in *W. Lossen*'s laboratory, isolated oxalohydroxamic acid from the reaction products of ethyl oxalate and hydroxylamine[1]. Later, when *W. Lossen* obtained a mixture of mono-, di-, and tribenzoyl derivatives from the reaction of hydroxylamine with benzoyl chloride, an era of tedious structural investigation commenced which was plagued by polymorphism, stereoisomerism, and tautomerism[2]. The pioneering efforts of investigators like *A. Werner*, *Lauder W. Jones*, and *C. D. Hurd* paved the way for a clearer understanding of structure and reactions in hydroxamic acid chemistry. In the absence of spectral data, the structure of the oxo form *(1)* was difficult to establish; many experimentalists believed that the hydroximic acid structure *(2)* represented hydroxamic acids correctly and that *(2)* would also exhibit geometrical isomerism akin to oximes. In his review in 1943, *Yale* brought some order to the state of confusion existing in the literature of hydroxamic acids[3]. Considerable progress was achieved in the last 30 years in understanding the chemistry of acyl derivatives of hydroxylamine[4], particularly with the evolution of spectral methods.



(1) *(2)* *(3)*

(1a), R = C_6H_5

Hydroxamic acids occupy relatively little space in textbooks. A noted exception is the Lossen rearrangement leading to isocyanates, which is usually mentioned as an appendage to the related Hofmann, Curtius, Schmidt, and Tiemann rearrangements[4]. Complexation of metal ions by hydroxamic acids is the basis of a number of analytical determinations[5]. The best known of these complexes is that with Fe^{3+} whose beautiful purple color forms the basis for the sensitive qualitative and quantitative determination of carboxylic acids and their derivatives[6,7].

This quick color test retains some value in the preparative work with hydroxamic acids and is unique for hydroxamic acids of structure *(1)*, although hydroxamic acids possessing either an NH or OH group may exhibit a red color with Fe^{3+} ion.

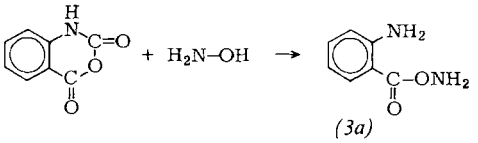
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2. Structure of Hydroxamic Acids

Monoacylation of hydroxylamine should produce *N*- and *O*-derivatives, *(1)* and *(3)*, respectively. Members of both series are known, but thermodynamically controlled reactions usually yield only *(1)*.

2.1. *O*-Acylhydroxylamines *(3)*

It was shown in 1942 that hydroxylaminolysis of isatoic anhydride produces *O*-(2-aminobenzoyl)hydroxylamine *(3a)*[8], the first identified representative of class *(3)*, although the classical Wöhler synthesis produces both *N*-hydroxyurea *(1)*, R = NH_2, and "isohydroxyurea" *(3)*, R = NH_2. The structure of the latter was proved by chemical methods to be *O*-carbamoylhydroxylamine[9a], and this structure was confirmed recently by X-ray analysis[10].



(3a)

Acylations of hydroxylamines frequently provide the primary kinetically controlled product *(3)*, which rearranges rapidly, particularly under the catalytic effect of hydroxylamine (α-effect)[9,11], to the thermodynamically stable hydroxamic acid *(1)*. Although it is possible to prove the structure of *(3)* by further acylation and subsequent Lossen rearrangements[8,9a], one can now readily distinguish between *(1)* and *(3)* by IR spectroscopy. The carbonyl stretching frequency in *(3)* is considerably higher (1760—1730 cm^{-1}) than that for the more amidic type of C=O in *(1)* (1670—1640 cm^{-1})[9b,12,13c]. Syntheses of *O*-acylhydroxylamines *(3)* are still being investigated and ingenious methods have been devised to prepare these types of compounds[9,13].

2.2. Hydroxamic Acids ("*N*-Acylhydroxylamines") *(1)*

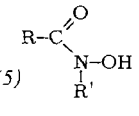
Structure *(1)* represents hydroxamic acids in the solid state, as shown by X-ray analyses of crystalline acetohydroxamic acid hemihydrate[14] and *N*-hydroxyurea[15]. All spectral evidence indicates that *(1)* is the predominant species in solutions. Attempts to detect even minute amounts of the tautomeric oximino form *(2)* in solutions failed. UV studies on hydroxamic acids and the monoalkyl derivatives of type *(4)* and *(5)* support structure *(1)*[16], which is further substantiated by the C=O stretching frequency in their IR spectra[12,17]. Furthermore, ESR[18], mass[19], and NMR[20] spectra of hydroxamic acids agree with structure *(1)*.



(4)

(4a)

(4b), R = CH_3, R' = Alkyl
(4c), R' = CH_3
(4d), R = C_6H_5, R' = CH_3
(4e), R = C_6H_5, R' = Alkyl



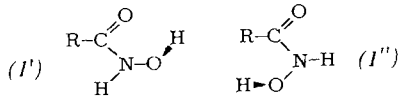
(5)

(5a), R = R' = C_6H_5
(5b), R = CH_3, R' = Alkyl
(5c), R' = CH_3
(5d), R = C_6H_5, R' = CH_3

Direct proof for the NH grouping in (1) was obtained only recently[20d] from the NMR spectrum of *p*-nitrobenzohydroxamic[^{15}N] acid in dimethyl sulfoxide, where a large spin-spin coupling constant between ^{15}N and H, $J_{N-H} = 102$ Hz, was observed[20d].

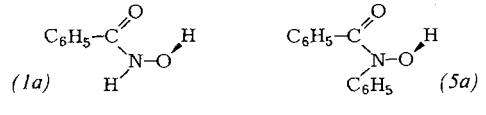
By way of comparison, thiohydroxamic acids are now believed to exist in the thioacylhydroxylamine form, R—CS—NHOH, both in solution and the solid state[20e,g]. Along those lines, it is interesting to note that amidoximes exist primarily as amino-oximino tautomers, R—C(=NOH)NH_2[20h]. All these types of molecules are strongly hydrogen bonded.

In the hydroxamic acid molecule (1) the oxygen, carbon, and nitrogen atoms belonging to the —C(O)—NO grouping are expected, by analogy with amides, to be in one plane; *a priori*, the OH group could assume two different spatial positions with respect to the C=O group: (1') and (1''). The NH—OH grouping is clearly not planar[14,15,21a]; for instance benzohydroxamic acid (1a) in dioxane approaches (1')[21a]. This conclusion was reached by determining the dipole moments of benzohydroxamic acid and suitable derivatives and by calculating dipole moments of these substances from suitable bond moments and angles[21].



(1') (1'')

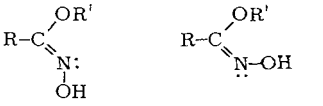
A similar conformation is postulated for the *N*-phenyl derivative (5a)[23]. No intramolecular hydrogen bond O—H···O is present in the crystal[14], probably due to unfavorable steric conditions, whereas such a bond is detected in dilute solutions by IR spectroscopy. This also explains the low C=O frequency[12,17c].



(1a) (5a)

Attempts to detect restricted rotation around the C⋯N bond of (1) due to partial carbon-nitrogen double bond character have not borne fruit. However, slightly restricted rotation about the C⋯N bond is reported for the highly substituted compound (10a) (see Section 3)[20b]. In a more recent report, NMR spectra of formohydroxamates HCO—N(R)OR' at low temperature clearly revealed restricted rotation about the C⋯N bond. The configuration of the rotamers was established by means of long range coupling constants[20g].

In order to study torsion about an N—O bond, the NMR spectra of 1-isopropoxy-2-pyridone (4a), a cyclic hydroxamate, were examined and a certain barrier to rotation was found[22].



(E)-(6) (Z)-(6)

(6a), R = C_6H_5, R' = $C_6H_5CH_2$
(6b), R' = C_2H_5
(6c), R = C_6H_5, R' = C_2H_5

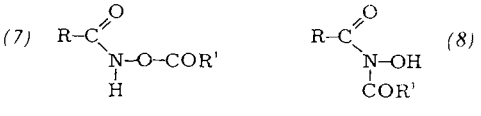
Since neither tautomerism nor partial double bond (C⋯N) character is detected in (1), the configurations of the N—OH group pose no structural problem. A configurational problem arises, however, when fixed C=N bonds are present, as in structure (6): (*E*) and (*Z*) isomers of type (6) have been differentiated by dipole moment measurements[26] which reversed the original literature assignments. These results were confirmed by X-ray analysis[24]. Dipole moment or NMR determinations were also useful in establishing the (*E*) and (*Z*) isomers of related *S*-alkyl thiohydroximates RC(=NOH)-SR'[25a,25b] and *O*-methylarenohydroximoyl chlorides ArC(=$NOCH_3$)Cl[25c].

3. Nomenclature

The hydroxamic or carbohydroxamic acid nomenclature (IUPAC Rule C-451.3) may be used for (1). For example, CH_3CO—NHOH is named acetohydroxamic acid, *cyclo*-$C_6H_{11}CO$—NHOH, cyclohexanecarbohydroxamic acid, and 1,4-$C_{10}H_6(CO—NHOH)_2$ 1,4-naphthalenedicarbohydroxamic acid. Alternatively, compound of type (1) may be named as *N*-hydroxycarboxamides according to Rule C 841.3.

Monoalkyl derivatives (4) and (5) are esters and *N*-substituted hydroxamic acids, respectively; for example (4b), CH_3CO—NHOAlkyl can be designated as alkyl acetohydroxamates (or *N*-alkoxyacetamide) and (5b), CH_3CON(Alkyl)OH, as *N*-alkylacetohydroxamic or *N*-alkyl-*N*-hydroxyacetamide.

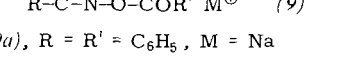
Compounds of type (6) are best named as derivatives of hydroximic acids (2). For example, (*Z*)-(6a) would be benzyl (*Z*)-benzohydroximate.



(7) (8)

(7a), R = R' = CH_3
(7b), R = R' = C_6H_5

(8a), R = R' = CH_3



(9)

(9a), R = R' = C_6H_5, M = Na
(9b), R = $(C_6H_5)_3C$, R' = CH_3, M = K

The acyl derivatives (7) and (8) can be named as hydroxamic acid derivatives, *e.g.* (7a) and (8a) as acetohydroxamic acetic anhydride and *N*-acetylacetohydroxamic acid, respectively. This type of name is preferred to those such as *O*,*N*-diacetylhydroxylamine and *N*-hydroxydiacetylamine, which infer that

these compounds are bases. Salts of *(7)* [*viz. (9)*] can then be named as hydroxamates.



(10) *(11)*

(10a), R = C_6H_5, R' = C_6H_5CO, R'' = $C_6H_5CH_2$

(10b), R = R' = R'' = CH_3

(10c), R = C_6H_5

(11a), R = C_6H_5

Dialkyl derivatives *(10)* are referred to as hydroxamates (*i.e.*, as esters). Therefore, *(10b)* can be named methyl *N*-methylacetohydroxamate; the possible names derived from *N*-hydroxyamides should also be borne in mind.

Like *(6)*, compounds *(11)* are derivatives of hydroximic acid; however, they can also be named as *N*-hydroxyimidic acid derivatives in analogy with the *N*-hydroxyamide nomenclature of hydroxamic acid derivatives.

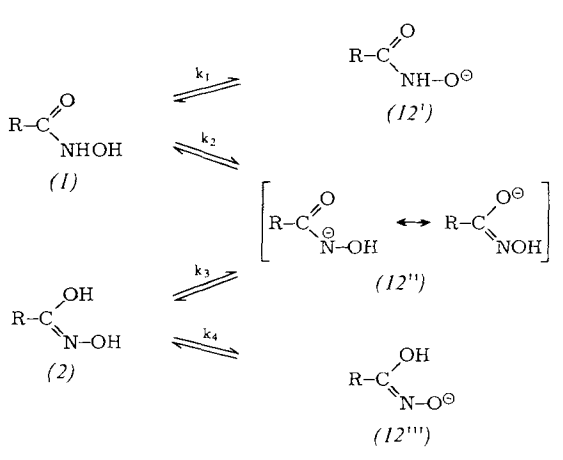
No attempt will be made to include the nomenclature of cyclic hydroxamic acids in which the functional groups become part of a heterocyclic system[4d, 27].

4. Ionization of Hydroxamic Acids *(1)*

4.1. Structure of the Hydroxamate Anion *(12)*

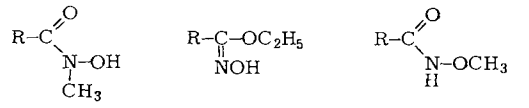
The unexpected relatively high acidity of hydroxamic acids *(1)* is one of their most striking properties. A number of pK_a values for RCO—NHOH are reported in the literature[28, 29] and these are of the order of 9 pK units, *i.e.*, approximately 6 units more acidic than amides $RCONH_2$. It should be noted that the difference between $NH_4^{\oplus}$ and $NH_3OH^{\oplus}$ is of the order of 3 pK units only. In a recent paper, the thermodynamic ionization constants were determined for a number of *p*-substituted benzohydroxamic acids and were found to correlate well with those calculated using Hammett's constants[28g, 29a].

The structure of the anion *(12)* is still the subject of some controversy. *A priori*, three possibilities *(12')*, *(12'')*, and *(12''')* are considered[29], and the ultimate aim is to determine



the four partial dissociation constants k_1 to k_4. At this point it is difficult to generalize beyond one hydroxamic acid and the solvent systems used for the particular study. Another difficulty lies in the detection of minute fractions; this problem also hindered the tautomerism studies alluded to in Section 2.2.

Nevertheless, some evidence has accumulated that *(12'')* best represents the structure of the anion of *(1)*. Measurements of dissociation constants could theoretically yield all the desired values k_1 to k_4 when the experimental pK values of such alkyl derivatives as *(5c)*, *(6b)*, and *(4c)* are considered as approximations of k_1, k_4 and $k_2k_3/(k_2+k_3)$, respectively[29]. This method can only lead to rather crude approximate values since the introduction of alkyl groups on N or O markedly effect these dissociation constants.



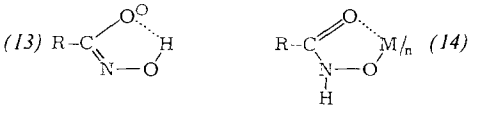
(5c) *(6b)* *(4c)*

(5d), R = C_6H_5 *(6c)*, R = C_6H_5 *(4d)*, R = C_6H_5

Although claims are made in the literature[29b, c] that the anions of aceto- and benzohydroxamic acids are composed of a mixture of *(12')* and *(12'')*, the proof based on UV measurements and pK_a values is not altogether convincing[29b, c, 30].

There is great disparity of values in the literature[29] resulting from pK_a determinations on hydroxamic acids *(1)* and their derivatives *(4)*, *(5)*, and *(6)*. For example, it would appear that benzohydroxamic acid *(1a)* and its methyl ester *(4d)* are stronger acids than *(5d)* or *(6c)*[29]. This is not unexpected, since resonance contributions [see *(12'')*] would enhance stabilization of the former, but not the latter two alkyl-substituted derivatives. In any one series, the acidity of either the NH or OH protons are affected to some degree by the nature of the substituents. For example, electron releasing substituents would reduce the relative acidity of the NH protons in *(4)* more than in *(5)*, since the inductive effect would be felt less by the more remote OH proton[5a, 29, 31].

An IR study of a salt of deuterated benzohydroxamic acid[31] in the solid state and in dioxane solution detected the O—D vibration frequency which could point to the presence of *(12'')* or, for that matter, *(12''')*. An intramolecular hydrogen bond, as in *(13)*, may also contribute to the stability of *(12'')*. An intramolecularly hydrogen-bonded species *(13)* could explain the stability of *(12'')* and the fact that nucleophilic reactions seem to take place preferentially on the NOH oxygen atom. The structure of complex salts of hydroxamic



(13) *(14)*

acids may differ from that of simple salts; the formula *(14)*[5] is supported already by the fact that *N*-alkylhydroxamic acids *(5)* form complexes, while *(4)* and *(6)* do not.

To summarize, the exact composition of salts of simple unsubstituted hydroxamic acids is not established with absolute certainty but there is good evidence that hydroxamic acids

bearing electron-attracting substituents dissociate exclusively to the anion *(12″)*, and thus belong to the *N*-acids.

4.2. Structure of the Hydroxamic Acid Cation

The structure of the cations of hydroxamic acids has received little attention, particularly since such salts are seldom isolated. Protonation of the carbonyl oxygen is suggested, by analogy with the behavior of amides; hence the cations are represented by the following formula[32]:

$$RC{=}\overset{\oplus}{O}H(NHOH) \leftrightarrow RC(OH){=}\overset{\oplus}{N}HOH$$

5. Reactions

It is not intended to survey all the reactions which have been reported for hydroxamic acids, but rather to restrict this section to recent studies in which the products have been well characterized.

5.1. Hydrolysis

Acid or base-catalyzed hydrolyses of hydroxamic acids *(1)* and their derivatives *(4)* or *(5)* to carboxylic acids and hydroxylamine derivatives proceed readily and it would appear logical to compare these hydrolyses with corresponding reactions of amides[29g, 32b, 32c]. Kinetic studies do indeed suggest that the mechanism of acid and base-catalyzed hydrolyses of benzohydroxamic acid resembles those of amides[32c].

By analogy to the hydrolysis of other carboxylic acid derivatives, the acid-catalyzed reaction is assumed to involve a cation whose structure is discussed in Section 4.2.

Attack by water leads to a tetrahedral intermediate of the kind usually associated with nucleophilic acyl substitution reactions; this intermediate yields the final products. First-order dependence on hydronium ion supports such a mechanism in a kinetic study of the hydrolysis of benzohydroxamic acid[32c]. For the acid-catalyzed hydrolysis of a number of aliphatic hydroxamic acids, polar and steric effects are found to be of comparable magnitude. This contrasts with the acid-catalyzed hydrolysis of amides or esters which show little or no dependence on polar effects. The observed rates correlate well with those calculated from the two-parameter Taft equation and thus support the above mechanism[29g].

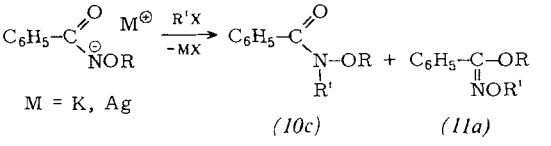
The base-catalyzed reaction is somewhat more complicated since the structure of hydroxamate anion *(12)* has not been settled. The question arises as to whether the unionized hydroxamic acid or its anion is attacked by hydroxide ion or water to produce the acid and hydroxylamine. Both first and second order dependence on hydroxide ion are inferred in the base-catalyzed reaction[32c], and further data are needed to establish these mechanisms.

5.2. Alkylation

Alkyl hydroxamates *(4)* are the major products resulting from the action of an alkylating agent on the hydroxamate ion *(12)*[33], in spite of the fact that three plausible sites exist for alkylation. One would expect the ambident anion *(12″)* to favor alkylation of the nitrogen or the carbonyl oxygen rather than the OH oxygen. However, the bifurcated anion species might be sufficiently hydrogen-bonded or coordinated to the accompanying cation that the oxygen attached to the nitrogen becomes the most nucleophilic and sterically least encumbered atom [see *(13)* and *(14)*] for attack on an electrophilic center.

The α-effect exerts a tremendous influence in effecting such a facile and selective reaction to form *(4)*. The anion *(12)* is rarely alkylated on the nitrogen to give *(5)*; these compounds are synthesized by another route, *viz.* acylation of R—NHOH[12, 33c–33e].

Further alkylation of *(4)* poses an interesting problem. The anion of *(4)* behaves more like an ambident anion and is subject to all the theories on this subject. The ratios of products are largely dependent upon the solvent, the nature of the accompanying cation, and the electrophilicity of the carbenium ion center in the alkylating agent. Alkylation of the potassium and silver salts of the alkyl esters C_6H_5CO—NHOR *(4e)* afforded a mixture of products from which the esters *(10c)* and the (*Z*) and (*E*) isomers of *(11a)* were isolated[33a]. The

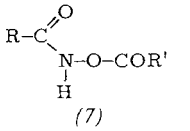


(10c) *(11a)*

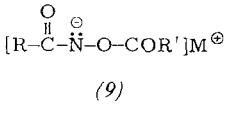
isomer distribution is very much influenced by the alkyl halide R′X, the solvent (DMF/R′OH), the structure of R′ and the nature of the leaving group X. The isomers did not isomerize during work up and were thus formed under kinetically controlled conditions. Although the authors advance theories compatible with current thoughts on S_N reactions involving ambident anions, there are no predictions regarding the major products arising from the alkylations of *(4)*[33a].

5.3. Acylation

The reaction of hydroxamic acids *(1)* with acid halides or anhydrides produces mixed anhydrides ("*O*-acylhydroxamic acids") *(7)*[34]. More reactive acid halides, however such as sulfonyl or phosphoryl halides induce an almost spontaneous Lossen rearrangement of *(1)* presumably *via* *O*-sulfonyl or *O*-phosphoryl derivatives (see Section 6). The mixed anhydrides *(7)* are acids (p*K* in water would be *ca.* 7[29a]); they form

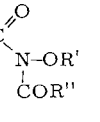


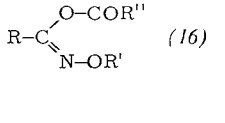
(7)



(9)

(15)





(16)

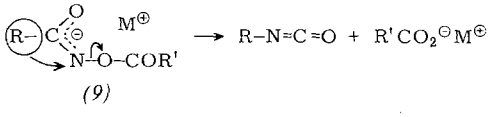
stable salts (in the cold) which rearrange on heating. Alkylation of these salts *(9)* and subsequent hydrolysis of the acyl residue produces either the (*Z*) or the (*E*) isomer of *(6)*[33a]. Acylation of the esters *(4)* yields the trisubstituted compounds *(15)*, and in certain instances also the isomers *(16)*[34c].

6. The Lossen Rearrangement

In 1872 *Lossen* discovered the rearrangement bearing his name when he observed that pyrolysis of the mixed anhydride *(7b)* affords phenyl isocyanate[2, 3]. This rearrangement does not take place with hydroxamic acids RCO—NHOH *(1)*, as is stated erroneously in some textbooks. Preliminary *O*-acylation is essential for a smooth rearrangement. Even then, such acyl derivatives only undergo pyrolytic rearrangement under fairly stringent conditions; *e.g.* *O*-(acetoacetyl)benzohydroxamic acids form isocyanates, acetone, and carbon dioxide only at 300—400 °C[34d].

The usual mode is to convert compounds *(7)* by means of a strong base (preferably in nonhydroxylic solvents) at low temperature into the salt *(9)*, preferably in a medium from which the salt precipitates. Rearrangement of the anion of *(9)* to the isocyanate involves the departure of the carboxylate ion with concomitant migration of the group R from carbon to nitrogen.

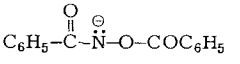
(7b) $C_6H_5-C(=O)-N(H)-O-COC_6H_5$



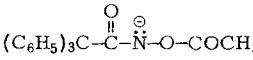
(9)

The rate of this base-catalyzed Lossen rearrangement depends upon the electronic nature of the groups R and R'. *Hauser*'s kinetic data relate the rate of rearrangement to the strength of the acid $R'CO_2H$[35]. Thus, the rate increases as the departing group $R'CO_2^{\ominus}$ becomes more electron-attracting. This explains why *O*-sulfonyl or *O*-phosphoryl hydroxamic acids cannot be isolated: they rearrange extremely rapidly in a basic milieu (see below).

In another study, it was demonstrated that the rearrangement is facilitated as the electron-releasing power of R in *(9)* increases, provided no undue steric effects enter the picture[36]. The stereospecificity of the Lossen rearrangement supports this concerted mechanism since it is proven that the configuration of R in *(7)* remains unchanged during the rearrangement[37]. All attempts to show that nitrene intermediates are involved in nonphotolytic rearrangements have been unsuccessful. The ionic pathway indicated above with concomitant movement of group R from C to N as the anion departs therefore represents the best picture for the mechanism[34e].



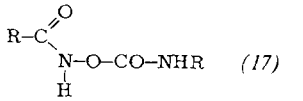
(9a)



(9b)

An example of the conventional rearrangement is that of *(9a)* in water at 95 °C to produce *N,N'*-diphenylurea. Presumably, the first product is phenyl isocyanate which hydrolyzes, in part, to aniline. The latter adds to residual isocyanate to produce the urea. As a matter of fact, *(9b)* is known to rearrange in water at room temperature to furnish trityl isocyanate.

Other activating groups inducing Lossen rearrangements have also been explored. 2,4-Dinitrofluorobenzene converts *(1)* into the *O*-2,4-dinitrophenyl derivatives, which rearrange in alkaline media to the amine RNH_2, 2,4-dinitrophenol, and carbon dioxide[38]. Another reagent for activating hydroxamic acids is sulfur trioxide (as the triethylamine complex) which forms the salts $RCO-NHOSO_3^{\ominus}$ $(C_2H_5)_3NH^{\oplus}$, in excellent yield. These derivatives are transformed into isocyanates, ureas, or urethanes under appropriate conditions[39].



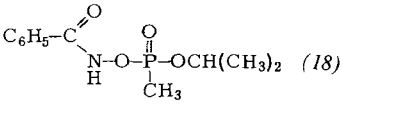
(17)

(17a), R = R' = C_6H_5

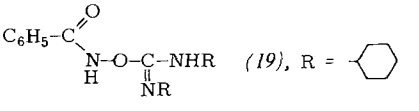
Unexpectedly, sulfonyl and phosphorus halides react vigorously with hydroxamic acids RCO—NHOH *(1)*. However, the products are not the *O*-sulfonyl or *O*-phosphoryl derivatives, but rather rearrangement products, *e.g.* *O*-carbamoyl hydroxamic acids *(17)*[40]. Thus, potassium benzohydroxamate is rearranged spontaneously by benzenesulfonyl chloride to give *(17a)* in one step.

A similar result is reported when benzohydroxamic acid *(1a)* was treated with the nerve gas "Sarin" (isopropyl methylphosphonofluoridate). In this reaction, the highly reactive intermediate *(18)* rearranges to phenyl isocyanate which in turn adds to unreacted benzohydroxamic acid to form *(17a)*.

The reaction of benzohydroxamic acid with benzenesulfonyl chloride or diisopropyl phosphofluoridate at pH 7.6 and 25 °C was investigated extensively in oxygen-18 labeled water[41]. The absence of oxygen-18 in any of the products expected from a Lossen rearrangement supports the mechanism involving initial formation of the *O*-sulfonyl- or *O*-phosphoryl hydroxamic acid. These hydroxamic acids then rearrange to phenyl isocyanate with simultaneous departure of the sulfonate *or* phosphate anion from the nitrogen. The isocyanate produced *in situ* now adds benzohydroxamic acid to produce the *O*-(phenylcarbamoyl)benzohydroxamic acid *(17a)*[41].

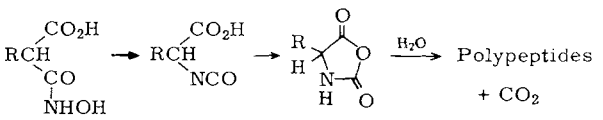


(18)



(19), R =

Interestingly, dicyclohexylcarbodiimide also reacts with benzohydroxamic acid to produce *(17a)*[42a]. The intermediate *(19)* from the addition of the hydroxamic acid to the diimide loses *N,N'*-dicyclohexylurea with concomitant rearrangement to phenyl isocyanate. Again isocyanate then adds a mole of benzohydroxamic acid to furnish the product. The rearrangement of the *anion* of *(17a)* is typical; the resulting carbamate anion loses CO_2 to yield aniline, which adds to phenyl isocyanate affording the isolated product *N,N'*-diphenylurea[42a]. An unusual Lossen rearrangement was observed when benzohydroxamic acid was treated with thionyl chloride, followed by thallium(I) phenoxide. The isolated triphenyl isocyanurate

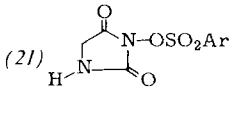


(20)

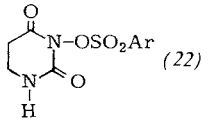
(23%) presumably arises from trimerization of phenyl isocyanate[42b].

Neighboring groups frequently react with an isocyanate group produced during a Lossen rearrangement. The Lossen degradation of half-malonohydroxamic acids *(20)* provides polypeptides, presumably *via* the route shown.

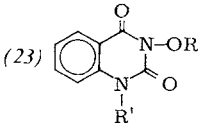
Since such polypeptides are prepared entirely in a basic medium, it becomes possible to synthesize an acid-sensitive polypeptide such as polytryptophan[43]. A hydroxamic acid group adds to a neighboring nitrile group when α-cyano esters react with hydroxylamine to form 5-amino-3-isoxazolones[44a]. Salicyclo- and anthranilohydroxamic acids react with benzenesulfonyl chloride to yield 2-benzoxazolone and 2-benzimidazolone, respectively[44]. Along these lines, a hydroxamic acid group can add to an adjacent isocyanate group to form a cyclic *N*-hydroxyimide. Thus, sulfonyl halides transform malonohydroxamic acids into *(21)*[45], and succino- and phthalohydroxamic acids into *(22)* and *(23a)* respectively[46].



(21)



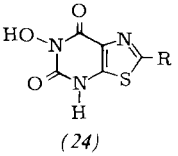
(22)



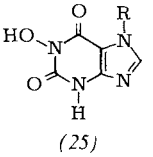
(23)

(23a), R = SO_2Ar, R' = H
(23b), R = $SO_2C_6H_5$, R' = H
(23c), R = $SO_2C_6H_5$, R' = CH_3

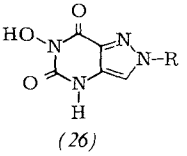
An extension of this method of fusing an *N*-hydroxyuracil ring onto five- or six-membered heteroaromatic systems resulted in the synthesis of various heterocycles of biochemical interest[47-51]. These include 3-hydroxylumazine, fused pyridopyrimidinediones, thiazolouracils, *e.g. (24)*, 1-hydroxyxanthines, *e.g. (25)*, and a number of *N*-hydroxypyrazolouracils represented by the selected structure *(26)*.



(24)



(25)



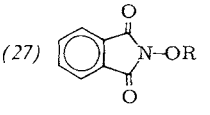
(26)

7. The Chemistry of Cyclic *N*-Hydroxyimides

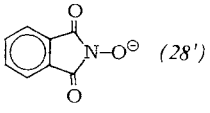
Cyclic *N*-hydroxyimides[52], particularly *N*-hydroxyphthalimide *(27a)*, have been known for a long time. Their synthesis has been discussed in Section 6. They may be formally regarded as *N*-acylhydroxamic acids of type *(8)*.

7.1. Structure and Alkylation

The assumption that *(27a)* exists in a colorless and a yellow modification proved to be erroneous. The yellow hue of the otherwise colorless crystals is caused by a minute amount of the intensely red anion *(28)*. One would expect the anion *(28')* of *N*-hydroxyphthalimide to be colorless [like the anion of *N*-hydroxysuccinimide]. It has therefore been suggested that the contribution of the highly chromophoric isomer *(28'')* is responsible for the intense color. In aqueous medium, the red solution of the salts of *N*-hydroxyphthalimide turns colorless due to their hydrolysis to *(29)*. The identity of *(29)* is established by its deep purple coloration with ferric chloride and by its isolation as the hydroxylammonium salt[52c]. Furthermore, *(29)* can be degraded by benzenesulfonyl chloride to anthranilic acid[52c].

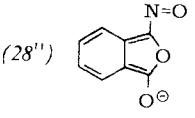


(27)

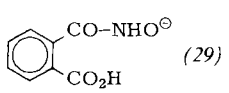


(28')

(27a), R = H
(27b), R = SO_2Ar



(28'')

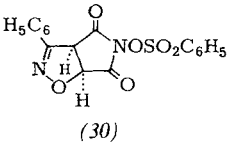


(29)

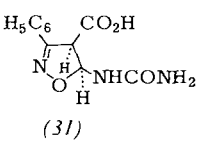
The stable triethylammonium salt of *(28')* can be alkylated in benzene to furnish *N*-alkoxyphthalimides, which readily yield *O*-alkylhydroxylamines on acid hydrolysis[53].

7.2. The Lossen Degradation of *N*-Hydroxyimides

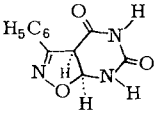
Although hydroxamic acids RCO—NHOH *(1)* fail to form stable *O*-sulfonyl derivatives, *N*-hydroxyimides form isolable *N*-sulfonyloxy and *N*-phosphoryloxy derivatives[52,54]. The Lossen rearrangement of these sulfonates to amino acids has been performed for aliphatic and aromatic systems. Thus reaction of *cis*-*N*-benzenesulfonyloxyhexahydrophthalimide with 10% aqueous NaOH solution produced *cis*-2-aminocyclohexanecarboxylic acid which is isolated as the benzenesulfonate[37c]. *N*-Sulfonyloxyphthalimides *(27b)* are degraded by amines to anthranilic acid derivatives[52,54a]. By a similar mechanism, *N*-benzenesulfonyloxynaphthalimide is converted by hydroxide ion to naphthostyril[55]. In the same vein, *cis*-*N*-benzenesulfonyloxy-3-phenyl-2-isoxazoline-4,5-dicarboximide *(30)* reacts with aqueous ammonia to yield only one ureido acid *(31)* which was further cyclized, in a separate step, by dilute hydrochloric acid to *(32)*[56].



(30)



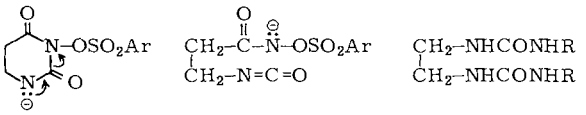
(31)



(32)

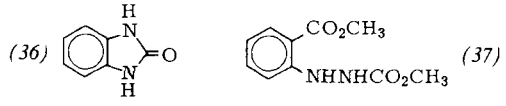
Interesting Lossen rearrangements are observed with *(22)*: treatment with one equivalent of NaOH produces ethylenediamine[46b], and degradative reduction to *N*,*N'*-dimethylethylenediamine occurs with $LiAlH_4$[57]. Both rearrangements are initiated by formation of *(33)* [the anion of *(22)*] which opens to give the anion *(34)* of *O*-arenesulfonyl-3-isocyanatopropionohydroxamic acid. The latter is the logical precursor for 1,2-ethylenediisocyanate, which can be hydrolyzed to ethyl-

enediamine or reduced to *N,N*-dimethylethylenediamine. The reaction of *(22)* with ammonia or amines produces ureas *(35)*, presumably *via* the diisocyanate[58].



(33) *(34)* *(35)*

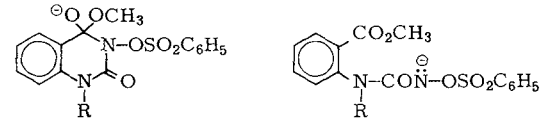
In a series of surprising Lossen rearrangements, 3-benzenesulfonyloxy-2,4-quinazolinedione *(23b)* rearranges either to benzimidazolone *(36)* or *o*-hydrazinobenzoic acid derivatives *(37)*[59a].



(36) *(37)*

The reaction of *(23b)* with NaH in DMF yields *(36)*. Presumably, neutralization of the acidic ring NH proton forms the anion [cf. *(33)*] which opens to produce *O*-benzenesulfonyl-2-isocyanatobenzohydroxamic acid. The latter rearranges to phenylene diisocyanate, from which *(36)* is created.

Lossen degradation to *(37)* is brought about by sodium methoxide in methanol. Attack by methoxide ion at the highly electrophilic C-4 atom of *(23b)* gives rise to a tetrahedral intermediate *(38a)* which opens to form *(39a)*. This second intermediate then rearranges to give *(40a)* which can add methanol to furnish *(37)*.



(38) *(39)*

(38a), R = H *(39a)*, R = H



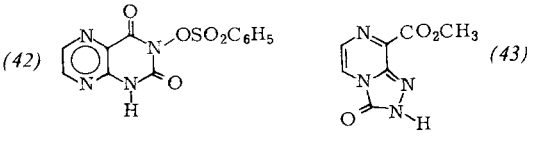
(40) *(41)*

(40a), R = H

It was therefore not surprising that the 1-methyl analog of *(23b)* [*(23c)*] is degraded by methoxide ion to 1-methyl-3-indazolone derivatives *(41)*, R = H or CO_2CH_3[59].

When the *pyridine* analogs of *(23a)* are treated with sodium methoxide, a series of *pyridine* analogs of *(37)* is obtained[59b]. An unusual product is encountered when the *pyrazine* analog *(42)* is exposed to sodium methoxide in methanol: the triazolopyrazine *(43)* is formed.

The mechanism of this reaction follows that suggested for the transformation of *(23)* into *(40)*, with the difference that

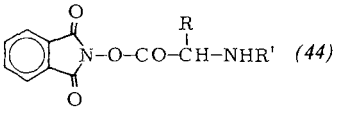


(42) *(43)*

the isocyanate cyclizes onto the pyrazine ring nitrogen in preference to adding methanol.

7.3. *N*-Hydroxyimides in Peptide Syntheses

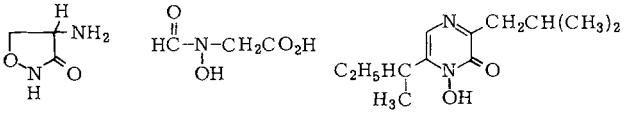
A number of investigators have explored the use of *N*-acyloxyimides as precursors for peptide syntheses[60]. The method commences with the preparation of esters of amino acid derivatives *(44)*, followed by attack by another amino acid on the activated ester carbonyl group to form a peptide link, with release of the *N*-hydroxyimide anion.



(44)

8. Brief Survey of Some of the Biological Activities of Hydroxamic Acids

Recent progress in hydroxamic acid chemistry has been stimulated by the isolation of several naturally occurring and the synthesis of a number of medicinally active hydroxylamine derivatives[4d]. Notable among these are the antibiotic cycloserine *(45)*[61], the antitumor antibiotic hadacidin *(46)*[62], and the heteroaromatic antibiotic aspergillic acid *(47)*[63].



(45) *(46)* *(47)*

A wide spectrum of biological activities has been reported and a full recent review exists[4d]. A few recent examples will now be considered. A series of *o*-, *m*-, and *p*-alkoxybenzohydroxamic acids was found to be highly effective against pathogenic fungi[64], while salicohydroxamic acids and derivatives are effective antibacterial and antifungal agents[65]. β-Alkylaminopropionohydroxamic acids show hypotensive properties[66], and a number of hydroxamic acids and *N*-hydroxyureas possess hypocholesteremic activity[67]. *p*-Butoxyphenylacetohydroxamic acid (Bufexamac) is in actual use as an antiinflammatory agent in humans[68]. A series of terephthalohydroxamic and other dicarbohydroxamic acids have been investigated as potential antimalarials[69].

In a quantitative structure-activity relationship study, using the Hansch approach, a series of aliphatic and *m*- and *p*-substituted benzohydroxamic acids were investigated for their relative power to inhibit urease activity[72]. Among the alkylhydroxamic acids, maximum activity was observed with heptanohydroxamic acid *(1)*, R = C_6H_{13}, which the authors attribute to stereospecific "hydrophobic bonding". They concluded that electronic effects do not play a significant role in this activity. However, the steric effect of a bulky substituent becomes very clear in a series of aliphatic hydroxamic acids in which a phenyl group is moved along the fatty acid chain: a remarkable decrease of inhibitory power is observed as the phenyl group approaches the hydroxamic acid group.

Hydroxamic acids number among the few compounds effective as nucleophilic reactivators of sarin-inactivated chymotrypsin[71] or acetylcholine esterase[28d]. *N*-Hydroxyurea has been investigated extensively since it exhibited antileukemic activity in mice and spurred extensive pharmacological screening of many *N*-hydroxyureas and urethans[4d]. Hydroxyurea (Hyd-

rea) is available to the medical profession as an approved drug for the treatment of melanoma, myelocytic leukemia, and carcinoma of the ovary[70].

One of the metabolites of the carcinogenic *N*-(2-fluorenyl)acetamide is *N*-(2-fluorenyl)acetohydroxamic acid[72]. This points to the potentially important biological oxidation of amides by *N*-hydroxylation and it is conceivable that other compounds containing monosubstituted amide groups can form similar metabolites.

9. Conclusions

While tremendous progress has been made over the past 30 years in understanding and applying the chemistry of hydroxamic acids and *N*-hydroxyimides, a number of problems remain to be solved. Although the structures of hydroxamic and hydroximic acids and derivatives are fairly well established, the fine structure of the anion of hydroxamic acid, as well as its hydrolysis and behavior on nucleophilic substitution, remain to be clarified. Perhaps, the greatest endeavor in the next decade will be in the area of the biological evaluation of hydroxamic acid derivatives. In the meantime the study of hydroxamic acids will remain a viable part of chemistry[*].

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German version: Angew. Chem. *86*, 419 (1974)

[*] *Note added in proof* (May 24, 1974): Meanwhile an interesting rearrangement of *N*-hydroxyureas to *O*-carbamoylhydroxylamines, in solution, has been reported:
RNH—CO—NR'OH ⇌ [RNHOH + R'NCO] → RNH—CO—ONHR'
The reaction has been shown to proceed *via* the sterically induced dissociation of the urea to a hydroxylamine and an isocyanate which recombine to give the product [*H. G. Aurich* and *H.-G. Scharpenberg*, Chem. Ber. *106*, 1881 (1973)].

[1] *H. Lossen*, Liebigs Ann. Chem. *150*, 314 (1869).

[2] *W. Lossen*, Liebigs Ann. Chem. *161*, 347 (1872); *186*, 1 (1877); *252*, 170 (1889); *281*, 169 (1894).

[3] *H. L. Yale*, Chem. Rev. *33*, 209 (1943).

[4] a) *F. Mathis*, Bull. Soc. Chim. Fr. *D 1953*, 9; b) *F. Mathis, R. Mathis-Noel, A. Chauveau*, and *A. Munoz*, Ann. Fac. Sci. Univ. Toulouse Sci. Math. Sci. Phys. *25*, 125 (1961); c) *O. Exner*, Dan. Tidsskr. Farm. *42*, 145 (1968); d) *R. T. Coutts*, Can. J. Pharm. Sci. *1*, 27 (1967); e) *P. A. S. Smith*: The Chemistry of Open-Chain Organic Nitrogen Compounds. Benjamin, New York 1966, Vol. 2, p. 68; f) *S. R. Sandler* and *W. Karo*: Organic Functional Group Preparation. Academic Press, New York 1972, Vol. VIII, p. 406.

[5] a) *S. Mizukami* and *K. Nagata*, Coord. Chem. Rev. *3*, 267 (1968); b) *T. J. King* and *P. G. Harrison*, J. C. S. Chem. Comm. *1972*, 815.

[6] *F. Feigl*: Spot Tests in Organic Analysis. Elsevier, Amsterdam 1966. 7th Edit., p. 214; *R. E. Buckles* and *C. J. Thelen*, Anal. Chem. *22*, 676 (1950); *E. Gagliardi* and *H. Raber*, Monatsh. Chem. *93*, 360 (1962); *D. W. Knight* and *G. H. Cleland*, J. Chem. Educ. *47*, 781 (1970); *A. K. Majumdar*: *N*-Benzoylphenylhydroxylamine and Its Analogues. Pergamon, Oxford 1972.

[7] A variation of this test is the Angeli-Rimini reaction in which aldehydes are transformed into hydroxamic acids by benzenesulfohydroxamic acid, $C_6H_5SO_2NHOH$ [see *G. Di Maio* and *P. A. Tardella*, Gazz. Chim. Ital. *96*, 526 (1966)].

[8] *A. W. Scott* and *B. L. Wood, Jr.*, J. Org. Chem. *7*, 508 (1942).

[9] a) *O. Exner*, Collect. Czech. Chem. Commun. *22*, 335 (1957); *23*, 272 (1958); b) *W. P. Jencks*, Biochim. Biophys. Acta *27*, 417 (1958); J. Amer. Chem. Soc. *80*, 4581, 4585 (1958); c) *T. C. Bruice* and *L. R. Fedor*, *ibid. 86*, 738, 739 (1964); d) *H. Kofod*, Acta Chem. Scand. *11*, 1276 (1957).

[10] *I. K. Larsen*, Acta Chem. Scand. *22*, 843 (1968).

[11] *W. P. Jencks* and *J. Carriuolo*, J. Amer. Chem. Soc. *82*, 1778 (1960); *J. D. Aubort* and *R. F. Hudson*, Chem. Commun. *1970*, 937, 938.

[12] *M. Davies* and *N. A. Spiers*, Spectrochim. Acta *15*, 487 (1959); *J. P. Freeman*, J. Amer. Chem. Soc. *80*, 5954 (1958); *O. Exner* and *M. Horak*, Collect. Czech. Chem. Commun. *24*, 968, 2992 (1959); *O. Exner* and *B. Kakac*, *ibid. 28*, 1656 (1963); *R. T. Coutts, K. W. Hindmarsh, S. J. Powell, J. L. Pound*, and *E. M. Smith*, Can. J. Pharm. Sci. *3*, 49 (1968).

[13] a) *W. N. Marmer* and *G. Maerker*, J. Org. Chem. *37*, 3520 (1972); b) *Y. Tamura, J. Minamikawa, K. Sumoto, S. Fujii*, and *M. Ikeda*, *ibid. 38*, 1239 (1973); c) *G. Zinner*, Arch. Pharm. *293*, 657 (1960); *L. A. Carpino, C. A. Giza*, and *B. A. Carpino*, J. Amer. Chem. Soc. *81*, 955 (1959).

[14] *B. H. Bracher* and *R. W. H. Small*, Acta Crystallogr. *26 B*, 1705 (1970).

[15] *I. K. Larsen* and *B. Jerslev*, Acta Chem. Scand. *20*, 983 (1966).

[16] a) *R. E. Plapinger*, J. Org. Chem. *24*, 802 (1959); b) *O. Exner* and *J. Holubek*, Collect. Czech. Chem. Commun. *30*, 940 (1965).

[17] a) *F. Mathis*, C. R. Acad. Sci. *232*, 505 (1951); b) *E. M. Usova* and *E. M. Voroshin*, Dokl. Akad. Nauk SSSR *113*, 1306 (1957); *114*, 120 (1957); c) *D. Hadzi* and *D. Prevorsek*, Spectrochim. Acta *10*, 38 (1957).

[18] *C. J. W. Gutch* and *W. A. Waters*, J. Chem. Soc. *1965*, 751; *D. F. Minor, W. A. Waters*, and *J. V. Ramsbottom*, J. Chem. Soc. *B 1967*, 180.

[19] *J. H. Bowie, M. T. W. Hearn*, and *A. D. Ward*, Aust. J. Chem. *22*, 175 (1969).

[20] a) *D. Snobl* and *O. Exner*, Collect. Czech. Chem. Commun. *34*, 3325 (1969); b) *B. J. Price* and *I. O. Sutherland*, Chem. Commun. *1967*, 1070; c) *K. Nagata* and *S. Mizukami*, Chem. Pharm. Bull. *14*, 1255 (1966); d) *O. Exner* and *D. Snobl*, unpublished; e) *V. N. Kalinin* and *I. F. Franchuk*, Zh. Org. Khim. *1972*, 1474; f) *W. Walter* and *E. Schaumann*, Synthesis *1971*, 111; g) Liebigs Ann. Chem. *743*, 154 (1971); h) *C. L. Bell, C. N. V. Nambury*, and *L. Bauer*, J. Org. Chem. *29*, 2873 (1964).

[21] a) *O. Exner*, Collect. Czech. Chem. Commun. *30*, 652 (1965); b) *O. Exner* and *O. Schindler*, Helv. Chim. Acta *52*, 577 (1969).

[22] *M. Raban* and *D. Kost*, J. Org. Chem. *37*, 499 (1972).

[23] *V. A. Granzhan, S. F. Manole, N. A. Barba*, and *S. K. Laktionova*, Izv. Akad. Nauk Mold. SSR, Ser. Biol. Khim., No. 2, 71 (1971).

[24] *I. K. Larsen* and *O. Exner*, Chem. Commun. *1970*, 254; *I. K. Larsen*, Acta Chem. Scand. *25*, 2409 (1971).

[25] a) *M. G. Waite* and *G. A. Sim*, J. Chem. Soc. *B 1971*, 752, 1102; b) *J. M. Davies, R. H. Davis*, and *P. Kirby*, J. Chem. Soc. *C 1968*, 431; c) *J. E. Johnson, E. N. Nalley*, and *C. Weidig*, J. Amer. Chem. Soc. *95*, 2051 (1973).

[26] *O. Exner, V. Jehlicka*, and *A. Reiser*, Collect. Czech. Chem. Commun. *24*, 3207 (1959).

[27] *P. N. Preston* and *G. Tennant*, Chem. Rev. *72*, 627 (1972).

[28] a) *W. M. Wise* and *W. W. Brandt*, J. Amer. Chem. Soc. *77*, 1058 (1955); b) *M. A. Stolberg* and *W. A. Mosher*, *ibid. 79*, 2618 (1957); c) *R. Swidler, R. E. Plapinger*, and *G. M. Steinberg*, *ibid. 81*, 3271 (1959); d) *W. Cohen* and *B. F. Erlanger*, *ibid. 82*, 3928 (1960); e) *A. L. Green, G. L. Sainsbury, B. Saville*, and *M. Stansfield*, J. Chem. Soc. *1958*, 1583; f) *G. Schwarzenbach* and *K. Schwarzenbach*, Helv. Chim. Acta *46*, 1390 (1963); g) *Y. K. Agrawal* and *J. P. Shukla*, Aust. J. Chem. *26*, 913 (1973).

[29] a) *O. Exner* and *W. Simon*, Collect. Czech. Chem. Commun. *30*, 4078 (1965); b) *J. Gerstein* and *W. P. Jencks*, J. Amer. Chem. Soc. *86*, 4655 (1964); c) *G. M. Steinberg* and *R. Swidler*, J. Org. Chem. *30*, 2362 (1965); d) *M. Dessolin* and *M. Laloi-Diard*, Bull. Soc. Chim. Fr. *1971*, 2946; e) *M. Dessolin, M. Laloi-Diard*, and *M. Vilkas*, *ibid. 1970*, 2573; f) *N. K. Dutt* and *T. Seshadri*, Bull. Chem. Soc. Jap. *40*, 2280 (1967); g) *D. C. Berndt* and *J. K. Sharp*, J. Org. Chem. *38*, 396 (1973).

[30] *A. R. Fields, B. M. Daye*, and *R. Christian*, Talanta *13*, 929 (1966).

[31] *O. Exner*, Collect. Czech. Chem. Commun. *29*, 1337 (1964).

[32] a) *O. Exner*, Collect. Czech. Chem. Commun. *21*, 1500 (1956); b) *A. J. Buglass, K. Hudson*, and *J. G. Tillett*, J. Chem. Soc. *B 1971*, 123; c) *D. C. Berndt* and *R. L. Fuller*, J. Org. Chem. *31*, 3312 (1966).

[33] a) *J. E. Johnson, J. R. Springfield, J. S. Hwang, L. J. Hayes, W. C. Cunningham*, and *D. L. McDlaugherty*, J. Org. Chem. *36*, 284 (1971); b) *W. B. Lutz*, *ibid. 36*, 3835 (1971); c) *W. Kliegel, G. Zinner, R. Vollrath, E. Duerkepf*, and *M. Hitze*, Liebigs Ann. Chem. *736*, 173 (1970); d) *M. T. W. Hearn* and *A. D. Ward*, Aust. J. Chem. *22*, 1731 (1969); e) *M. Chehata, F. Bocabeille, G. Thuillier*, and *P. Rumpf*, C. R. Acad. Sci. *C 268*, 445 (1969); f) *D. McHale, J. Green*, and *P. Mamalis*, J. Chem. Soc. *1960*, 225, 229.

[34] a) *O. Neunhoeffer* and *R. Gottschlich*, Liebigs Ann. Chem. *736*, 100 (1970); b) *A. I. Artemenko*, J. Org. Chem. USSR (Engl. Transl.) *7*, 724 (1971); c) *M. T. W. Hearn* and *A. D. Ward*, Aust. J. Chem. *22*, 161 (1969); d) *T. Mukayama* and *H. Nohira*, J. Org. Chem. *26*, 782 (1961); e) *A. Fry* and *J. C. Wright*, Chem. Eng. News *46*, No. 1, p. 28 (1968); *O. Exner*, Collect. Czech. Chem. Commun. *27*, 2284 (1962).

[35] *R. D. Bright* and *C. R. Hauser*, J. Amer. Chem. Soc. *61*, 618 (1939).

[36] *D. C. Berndt* and *H. Shechter*, J. Org. Chem. *29*, 916 (1964); *J. S. Swenson, A. M. Davis, R. E. Deyo, B. W. Graham, E. P. Jahn*, and *I. D. Mattice*, *ibid. 39*, 3956 (1973).

[37] a) *J. Kenyon* and *D. P. Young*, J. Chem. Soc. *1941*, 263; b) *J. F. Lane* and *E. S. Wallis*, J. Amer. Chem. Soc. *63*, 1674 (1941); c) *L. Bauer* and *S. V. Miarka*, J. Org. Chem. *24*, 1923 (1959).

[38] *P. M. Gallop, S. Seifter, M. Lukin*, and *E. Meilman*, J. Biol. Chem. *235*, 2619 (1960).

[39] *F. A. Daniher*, J. Org. Chem. *34*, 2908 (1969).

[40] a) *C. D. Hurd* and *L. Bauer*, J. Amer. Chem. Soc. *76*, 2791 (1954); b) *M. A. Stolberg, R. C. Tweit, G. M. Steinberg*, and *T. Wagner-Jauregg*,

ibid. 77, 765 (1955); c) *B. E. Hackley, Jr., R. Plapinger, M. Stolberg,* and *T. Wagner-Jauregg, ibid.* 77, 3651 (1955); d) *R. Swidler* and *G. M. Steinberg, ibid.* 78, 3594 (1956).

[41] *D. Samuel* and *B. L. Silver*, J. Amer. Chem. Soc. *85*, 1197 (1963).

[42] a) *K. Nagarajan, S. Rajappa,* and *V. S. Iyer*, Tetrahedron *23*, 1049 (1967); b) *E. C. Taylor* and *F. Kienzle*, J. Org. Chem. *36*, 233 (1971).

[43] *L. Bauer*, J. Org. Chem. *21*, 1182 (1956), and references to prior work.

[44] a) *L. Bauer* and *C. N. V. Nambury*, J. Org. Chem. *26*, 4917 (1961); b) *F. M. Hershenson, L. Bauer,* and *K. F. King, ibid. 33*, 2543 (1968).

[45] *G. Zvilichovsky*, J. Org. Chem. *34*, 486 (1969).

[46] a) *C. D. Hurd, C. M. Buess,* and *L. Bauer*, J. Org. Chem. *19*, 1140 (1954); b) *C. M. Buess* and *L. Bauer, ibid. 20*, 33 (1955).

[47] *L. Bauer, C. N. V. Nambury,* and *F. M. Hershenson*, J. Heterocycl. Chem. 3, 224 (1966).

[48] *K. Y. Tserng* and *L. Bauer*, J. Heterocycl. Chem. *9*, 1433 (1972).

[49] *L. Bauer, C. N. V. Nambury,* and *D. Dhawan*, J. Heterocycl. Chem. *1*, 275 (1964); *L. Bauer* and *D. Dhawan, ibid. 2*, 220 (1965).

[50] *L. Bauer* and *C. S. Mahajanshetti*, J. Org. Chem. *31*, 2491 (1966); J. Heterocycl. Chem. *4*, 325 (1967).

[51] *L. Bauer* and *C. S. Mahajanshetti*, J. Heterocycl. Chem. *5*, 331 (1968).

[52] a) *C. D. Hurd, C. M. Buess,* and *L. Bauer*, J. Org. Chem. *17*, 865 (1952); b) *19*, 1140 (1954); c) *L. Bauer* and *S. V. Miarka*, J. Amer. Chem. Soc. 79, 1983 (1957); d) *H. Gross* and *I. Keitel*, J. Prakt. Chem. *311*, 692 (1969); e) *C. D. Hurd* and *V. G. Bethune*, J. Org. Chem. *35*, 1471 (1970); f) *M. Narita, T. Teramoto,* and *M. Okawara*, Bull. Chem. Soc. Jap. *44*, 1084 (1971).

[53] *G. H. Hamor, D. M. Breslow,* and *G. W. Fisch*, J. Pharm. Sci. *59*, 1752 (1970); *D. M. Brown, P. F. Coe,* and *D. P. L. Green*, J. Chem. Soc. *C 1971*, 867; *L. Bauer, K. S. Suresh,* and *B. K. Ghosh*, J. Org. Chem. *30*, 949 (1965); *A. O. Ilvespää* and *A. Marxer*, Chimia *18*, 1 (1964).

[54] a) *E. Kühle* and *R. Wegler*, Liebigs Ann. Chem. *616*, 183 (1958); b) *T. M. Chapman* and *D. G. Kleid*, J. Org. Chem. *38*, 250 (1973).

[55] *V. L. Pladikin, N. M. Zadorozhnyi,* and *Z. I. Krasota*, J. Org. Chem. USSR (Engl. Transl.) *6*, 1480 (1970); *9*, 171 (1973).

[56] *W. J. Tuman* and *L. Bauer*, J. Org. Chem. *37*, 2983 (1972).

[57] *L. Bauer*, J. Amer. Chem. Soc. *78*, 1945 (1956).

[58] *L. Bauer*, unpublished results.

[59] a) *K. Y. Tserng* and *L. Bauer*, J. Org. Chem. *38*, 3498 (1973); b) Abstracts of 4th Int. Congress of Heterocyclic Chemistry, Salt Lake City, Utah, July 9, 1973, p. 59; J. Heterocycl. Chem. *11*, 163 (1974).

[60] Some recent applications can be found in the papers of *A. R. Zeiger* and *C. B. Anfinsen*, J. Amer. Chem. Soc. *95*, 880 (1973); *T. M. Chapman* and *D. G. Kleid*, J. Org. Chem. *38*, 250 (1973); *W. König*, Chem. Ber. *106*, 193 (1973); *R. Geiger* and *A. Volk, ibid. 106*, 199 (1973); *W. König* and *R. Geiger, ibid. 103*, 788 (1970); *V. A. Shibnev, T. P. Chuveava,* and *K. T. Poroshin*, Bull. Acad. Sci. USSR (Engl. Transl.) *1970*, 111; *K. T. Wang, D. N. Brattesani,* and *B. Weinstein*, J. Heterocycl. Chem. *3*, 98 (1966).

[61] *R. L. Harned, P. H. Hidy,* and *E. K. LaBaw*, Antibiot. Chemother. (Washington) *5*, 204 (1955); *D. A. Harris, M. L. Ruger, M. A. Reagan, F. J. Wolf, R. L. Peck, H. Wallick,* and *H. B. Woodruff, ibid. 5*, 204 (1955); for its preparation see also US-Pat. 2929836 (1960); Brit. Pat. 791847 (1958).

[62] *E. A. Kaczka, C. O. Gitterman, E. L. Dulaney,* and *K. Folkers*, Biochemistry *1*, 340 (1962).

[63] *J. D. Dutcher*, J. Biol. Chem. *171*, 321, 341 (1947).

[64] *J. Hase, K. Kobashi, N. Kawaguchi,* and *K. Sakamoto*, Chem. Pharm. Bull. *19*, 363 (1971).

[65] *N. Duda, A. Ostaszynski,* and *T. Urbanski*, Bull. Acad. Pol. Sci., Ser. Sci. *13*, 341 (1965).

[66] *R. T. Coutts, J. W. Hubbard, K. K. Midha,* and *K. Prasad*, J. Pharm. Sci. 60, 28 (1971).

[67] *B. J. Ludwig, F. Dürsch, M. Auerback, K. Tomeczek,* and *F. M. Berger*, J. Med. Chem. *10*, 556 (1967).

[68] *D. Dell, D. R. Boreham,* and *B. K. Martin*, J. Pharm. Sci. *60*, 1368 (1971).

[69] *J. B. Hynes* and *L. G. Hark*, J. Med. Chem. *15*, 1194 (1972); *13*, 1235 (1970).

[70] a) *C. W. Young, G. S. Schochetman, S. Hodas,* and *M. E. Balis*, Cancer Res. 27, 535 (1967); b) *B. Stearns, K. A. Losee,* and *J. Bernstein*, J. Med. Chem. 6, 201 (1963).

[71] *K. Kumaki, S. Tomioka, K. Kobashi,* and *J. Hase*, Chem. Pharm. Bull. *20*, 1599 (1972).

[72] *A. Goldstein, L. Aronow,* and *S. M. Kalman*: Principles of Drug Action. Harper and Row, New York 1969, pp. 691 ff.

Mass Transport in Solids

By Günther Heinz Frischat[*]

Two aspects are especially important in connection with mass transport in solids; these are the phenomenological description of the diffusion process and the discussion of the transport mechanism. In addition to the self-diffusion of the constituent ions or atoms of a solid, which can be followed only with the aid of radioactive or stable isotopes, other known types of diffusion are the diffusion of trace elements, which can in principle be treated in the same way as self-diffusion, and chemical diffusion, in which the diffusion partners differ in their chemical composition. Processes of this type are being increasingly studied with the electron beam microprobe. Regardless of the crystallinity and the type of bonding, problems concerned with diffusion in solids can be discussed from a single standpoint by slight adaptation to suit the particular situation in question.

1. Introduction

Diffusion processes in solids provide information about the mobility of the particles that constitute the solid or that react with it. In the former case, *i.e.* in self-diffusion, the intrinsic mobility of the atoms or ions is determined; an insight into the dynamic structure of solids can be gained from measurements on this process. In the second case, *i.e.* chemical diffusion, one follows true chemical reactions, exchange processes, *etc.* between one solid and another solid, a liquid, or a gas. Chemical diffusion and self-diffusion are uniquely related to each other.

It is not purely on their own account that diffusion processes are interesting. There are many processes in which mass transport of this nature is involved or is even rate-determining. Some examples are crystallization, oxidation or scaling processes, corrosion phenomena on metals or oxides under the

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action of melts or gases, and solid-state reactions such as cement formation and sintering, *etc.*

The first step in a diffusion study is the phenomenological description of the diffusion process. This is often very difficult because, except in the case of single crystals, the effects of higher-dimensional crystal imperfections such as dislocations, grain boundaries, and internal surfaces (pores and microcracks), as well as noncrystalline phases, must be taken into account. The next problem is to clarify the mechanism of the mass transport, *i.e.* the individual reaction steps taking place on the atomic scale in conjunction with the structure and the disorder of the solid. The two aspects are comparable in their importance.

It is also necessary to examine how these processes are affected by the bond character in the solid (*e.g.* metal, ionic crystal).

2. General Laws of Diffusion

For the present, diffusion will be regarded here as a process that leads to concentration leveling within a single phase. Since diffusion always involves at least two components, there are at least two diffusion equations to be considered, though in many cases it is sufficient to follow only one component explicitly[1-8].

Fick's laws form the basis for the mathematical description of diffusion processes. Fick's 1st law links the diffusion flux with the concentration gradient as the driving force:

$$\vec{J} = -D \operatorname{grad} c \tag{1}$$

$\vec{J}$ = diffusion flux [g cm^{-2} s^{-1}]; c = concentration [g/cm^3]; D = diffusion coefficient [cm^2/s].

The change in the concentration with time is described by Fick's 2nd law:

$$\frac{\partial c}{\partial t} = \operatorname{div}(D \operatorname{grad} c) \tag{2}$$

t = diffusion time [s].

In many experimentally realizable cases, a one-dimensional treatment in the x direction is sufficient. One then obtains

$$\frac{\partial c}{\partial t} = \frac{\partial (D \cdot \partial c/\partial x)}{\partial x} \tag{2a}$$

and for constant D this gives the usual form

$$\frac{\partial c}{\partial t} = D \cdot \frac{\partial^2 c}{\partial x^2} \tag{2b}$$

The solutions of eq. (2) depend on the particular initial and boundary conditions of the diffusion experiments. We shall first consider the case of a constant diffusion coefficient, *i.e.* eq. (2b). Two of the commonest cases in diffusion studies on solids have a point source and a step source respectively as initial conditions.

In studies with radioactive tracers (cf. Section 3.1), the diffusing substance is concentrated at the point $x=0$ at $t=0$; the initial and boundary conditions (point or instantaneous source) are then:

$$c(x,t) = \begin{cases} c_0 \delta(x) \text{ for } t=0 \\ 0 \text{ for } x \to \infty \text{ and } t \geq 0 \end{cases} \tag{3}$$

c_0 = initial concentration [g/cm^2]; $\delta(x)$ = Dirac's delta function

The solution of eq. (2b) is given under these conditions by the Gaussian function:

$$c(x,t) = \frac{c_0}{2\sqrt{\pi D t}} \exp(-x^2/4Dt) \tag{4}$$

A step source occurs *e.g.* when diffusion processes take place between two solids in contact with each other (cf. Section 3.2). The initial and boundary conditions are

$$c(x,t) = \begin{cases} C_0 \text{ for } x<0 \text{ and } t=0 \\ 0 \text{ for } x>0 \text{ and } t=0 \end{cases} \qquad \frac{\partial c}{\partial x} = 0 \text{ for } x \to \pm\infty \text{ and } t>0 \tag{5}$$

The solution of eq. (2b) is then given by

$$c(x,t) = \frac{C_0}{2}\left[1 - \operatorname{erf}\left(\frac{x}{2\sqrt{Dt}}\right)\right] \tag{6}$$

C_0 = initial concentration [g/cm^3]; erf(y) = Gaussian error function (listed *e.g.* in Ref. [3])

Solutions are also known for other geometric cases[1-8]. The experimenter's problem is initially to design the experiment as far as possible in such a way that one of the known solutions can be applied. It is only when the corresponding conditions cannot be realized that other solutions of the diffusion equations should be sought.

Eq. (2) was solved above on the assumption of a constant diffusion coefficient D. This assumption is never strictly valid, and is approximately valid only in limiting cases. It is particularly important to know the dependence of the diffusion coefficient on the concentration. One must therefore start with the general eq. (2) or (2a) with $D=D(c)$. The Boltzmann-Matano solution method[9,10] then leads, for the initial and boundary conditions in eq. (5) and for $t=$ const., to

$$D(c) = \frac{1}{2t}\frac{dx}{dc}\int_c^{c_0} x\,dc \tag{7}$$

It is physically obvious that all the matter that diffuses out of the half-space $x<0$ must be found later in the half-space $x>0$. The coordinate of the "Matano plane" $x_m=0$ can therefore be calculated from the equation

$$\int_c^{c_0} x\,dc = 0 \tag{8}$$

Only if the molar volume is constant does this coordinate coincide with the value $x=0$ for the original interface at the start of the experiment.

So far we have considered diffusion in a *single* phase. In systems with several phases, diffusion leads to leveling of the chemical potentials μ, or in the case of charged particles to leveling of the electrochemical potentials η. The driving forces, instead of a concentration gradient grad c, are then the potential gradients grad μ or grad η. At equilibrium

the μ or η values for the two phases are equal; no mass transport then occurs, even if the concentrations in the two phases are different. "Uphill diffusion" is therefore formally possible. Further complications in the evaluation of diffusion experiments on solids can arise *e.g.* from inhibitions at the phase boundary. The two phenomena may also occur together (for further information see Refs. [1—8]). *Wagner*[11] gives equations that allow an evaluation for $D(c)$ even when several phases are present.

3. Experimental Methods

In the study of diffusion in solids, the three-dimensional distribution of the diffused substances is usually determined experimentally to allow the calculation of the diffusion coefficient. The detection method to be used depends on the nature of the experiment and the required sensitivity.

Many physical and chemical detection methods have been developed over the years. Examples are X-ray absorption or fluorescence methods, optical methods, chemical methods of various kinds, methods involving the use of radioactive or stable isotopes, microhardness determinations, the use of the electron beam microprobe, and mass spectrometric, autoradiographic, or activation-analytical methods.

Two commonly used methods, one for the determination of self-diffusion and the other for the determination of chemical diffusion, will now be described in some detail.

3.1. Use of Radioactive Isotopes

The use of isotopes is essential for the determination of self-diffusion. There is no concentration gradient in self-diffusion. A large number of suitable isotopes are available, *e.g.* ^{14}C, ^{22}Na, ^{26}Al, ^{45}Ca, ^{59}Fe[12]. These emit γ or/and β rays, which can be followed with the aid of counters. Some α-active isotopes, *e.g.* ^{212}Pb, ^{210m}Bi, and ^{233}U, are also suitable. However, a number of important elements (oxygen, nitrogen, silicon, *etc.*) have no radionuclides that can be used. In such cases, one must turn to stable isotopes (^{18}O, ^{15}N, ^{30}Si, *etc.*) and their detection by relatively demanding activation-analytical (*e.g.* by the reaction $^{18}O(p,n)^{18}F$) or mass-spectrometric methods.

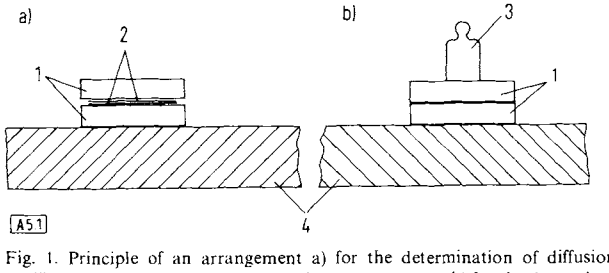


Fig. 1. Principle of an arrangement a) for the determination of diffusion coefficients with radionuclides (sandwich arrangement); b) for the determination of chemical diffusion (contact method). 1 = samples, 2 = tracer layers, 3 = weight, 4 = substrate.

Figure 1a shows the principle of the arrangement for diffusion determinations with radionuclides. The initial condition of a point source in eq. (3) is reasonably well satisfied by the tracer layer (*e.g.* a drop of $^{22}NaCl$ in aqueous solution, total quantity of ^{22}Na about 10^{-9} g), applied before the diffusion experiment, with a thickness of $< 3\,\mu m$. Each sample corresponds to a diffusion system that is unbounded on one side; this condition is satisfied in most cases by samples with a diameter of *e.g.* 2 cm and a thickness of 1 mm.

After the diffusion, *i.e.* the penetration of the radioactive particles into the solid, it is necessary to determine their distribution. This can be done in various ways. In the serial sectioning method, thin layers 50, 5, or 0.5 μm [depending on the penetration depth; special electrolytic microetching techniques even allow the removal of 100 Å layers (cf. *e.g.* Ref. [13])] are removed by grinding, etching, machining *etc.* The radioactivities of the individual layers are then determined. In the case of hard and brittle materials (hard metals, ceramics, glasses, *etc.*), it is preferable to measure the activity of the residual sample[14].

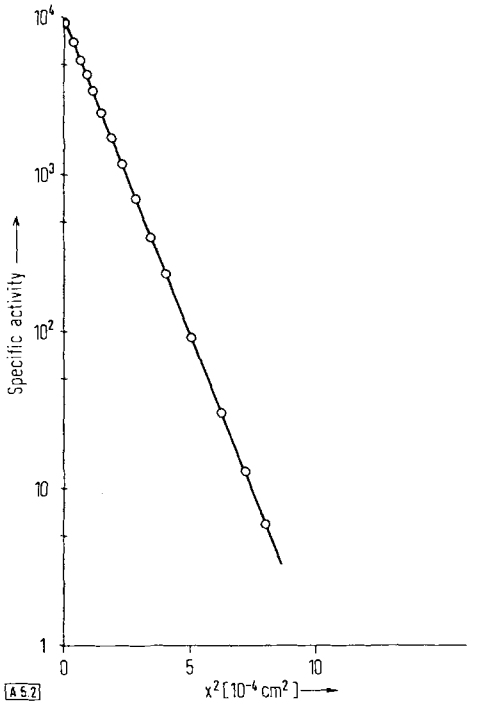


Fig. 2. Profile of the diffusion of ^{103}Pd in Pd single crystals. $T = 1148$ °C, $t = 242$ h [15]. The specific activity is given in arbitrary units. The diffusion coefficient is found to be $D = 3.15 \cdot 10^{-11}$ cm^2/s.

Figure 2 shows an example of the diffusion of ^{103}Pd in metallic Pd[15]. The penetration curve may be evaluated numerically with an automatic computer or graphically as in Figure 2. It can be seen immediately from eq. (4) that a plot of $\log c(x,t) = f(x^2)$ gives a straight line, from whose slope the diffusion coefficient is obtained. An absolute determination of the tracer concentration is unnecessary. This and similar types of plot are known as "diffusion profiles".

By this technique just described or by similar methods, it is possible to determine diffusion coefficients of between about 10^{-4} and 10^{-15} cm^2/s, and even as low as about 10^{-18} cm^2/s with the special microstripping techniques. Values down to 10^{-18} cm^2/s can also be measured when α-active nuclides are used[16]. It is clearly of no importance in this type of diffusion experiment whether the solid investigated is a metal, an ionic crystal, a glass, an organic crystal, *etc.* One simply makes corresponding changes in the preparation techniques.

3.2. Use of the Electron Beam Microprobe

In chemical diffusion, the diffusion partners normally differ in their chemical composition, and *e.g.* a new phase may

be formed on leveling by diffusion. To investigate a solid-state reaction[*] of this type, the two starting materials are pressed together under light pressure by the contact method, sealed together (*e.g.* glasses), *etc.* (cf. Fig. 1b). After a time, a reaction layer has formed between the starting materials, and this layer must be analyzed.

The electron beam microprobe is being increasingly used for the study of this and similar diffusion processes between solids or between melts and solids[17]. This instrument is based on the principle that a finely focused electron beam stimulates the emission of characteristic X-rays by the chemical elements at the point where it strikes the specimen. Both point analysis and line scanning of the samples are possible. This method allows the selection of sample volumes of a few μm^3 from the structure and their qualitative or quantitative analysis. Reference standards, for example, are necessary for quantitative analysis.

The elements between ^{5}B and ^{92}U can be detected; within this range, the nature of the solid (*e.g.* metal, ionic crystal) is of no importance. Diffusion coefficients of between 10^{-4} and 10^{-13} cm^2/s, and in special cases even lower values, can be determined.

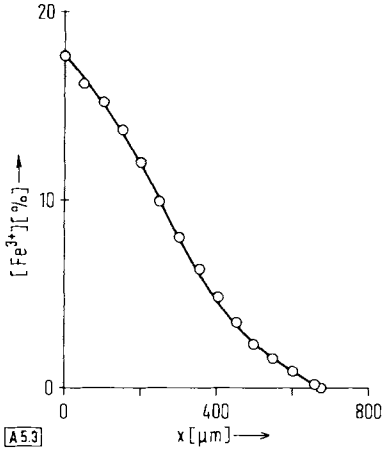


Fig. 3. Profile of the diffusion of Fe^{3+} (from Fe_2O_3) in MgO, $T = 1390$ C, $t = 66.5$ h [18].

Figure 3 shows the profile obtained in this way for the diffusion of Fe^{3+} ions in the binary system MgO—Fe_2O_3[18]. In every case, the evaluation also gives the concentration dependence of the diffusion coefficient (cf. Section 4.2).

4. Examples of Diffusion in Solids[**]

4.1. Self-Diffusion

4.1.1. Single Crystals

Nothing has been said so far about the structure of the substance in which diffusion occurs. We shall deal first with single crystals, which are characterized by a strictly regular structure and by the fact that they contain only zero-dimensional crystal defects (Frenkel or Schottky defects) that are present at thermal equilibrium. Effects due to higher-dimensional defects should be negligible. It has been known for a long time that diffusion processes are brought about by this intrinsic imperfection. This type of diffusion is known as lattice or volume diffusion.

There are numerous known examples of self-diffusion processes in single crystals of all kinds (see *e.g.* Refs. [19—24, 26]). The possibility of description by an unequivocal diffusion coefficient is an important characteristic (see also Fig. 2). In normal single crystals, all the sites that can be occupied by the migrating particles are energetically equivalent. However, if this situation is changed, *e.g.* for structural reasons (type A zeolite[27]), because of traps[*] (Bi[28]), or because of substitution and interstitial sites (SiC[29]), deviations occur.

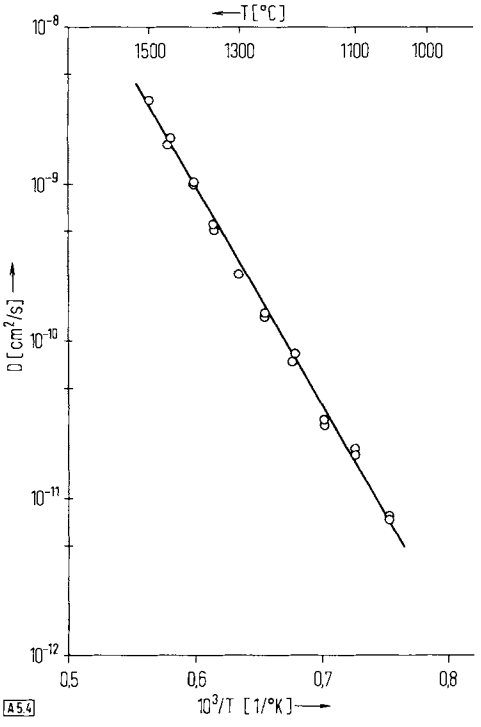


Fig. 4. Temperature dependence of the diffusion of ^{103}Pd in Pd single crystals, $T = 1057$ to 1503 C [15].

Figure 4 shows the temperature dependence of the diffusion of ^{103}Pd in Pd single crystals[15]. The values of the diffusion coefficient D are plotted according to the Arrhenius equation:

$$D = D_0 \exp(-Q/RT) \qquad (9)$$

D_0 = frequency factor [cm^2/s]; Q = activation energy [kcal/mol]; R = general gas constant [cal deg^{-1} $mole^{-1}$]; T = temperature [K].

The numerical values obtained are

$$D_0 = 0.205^{+0.05}_{-0.04}\ cm^2/s \text{ and } Q = 63.60 \pm 0.65\ kcal/mol.$$

The self diffusion coefficient of palladium between 1057 and 1503 °C is unequivocally fixed by these quantities.

[*] The term "solid-state reaction" refers here not only to chemical reactions but also to ion exchange processes.

[**] Values for diffusion in solids can be found *e.g.* in [2—8]. There are also a series of reviews on limited fields, *e.g.* on metals [19], oxides [20], carbides [21], halides [22], inorganic nuclear fuel materials [23], SiO_2 [24], and glasses [25]. Probably the most comprehensive collection of diffusion values is Diffusion Data [26], which started to appear in 1967. This collection contains results for metals, semiconductors, oxides, glasses, halides, refractory materials, organic crystals, *etc.*

[*] Traps are sites in the structure where particles can be enclosed immobile for some time.

Table 1. Examples of self-diffusion and diffusion of trace elements in single crystals. D_0 = frequency factor, Q = activation energy.

Substance	Isotope	Temp. range [°C]	D_0 [cm²/s]	Q [kcal/mol]	Ref.
Palladium	^{103}Pd	1057–1503	$0.205^{+0.05}_{-0.04}$	63.60 ± 0.65	[15]
AgCl	^{110}Ag	140–350	1.46	20.5	[30]
AgCl	^{36}Cl	324–443	$1.33 \cdot 10^2$	47.1	[30]
CoO	^{60}Co	963–1638	$(5.0 \pm 0.4) \cdot 10^{-3}$	38.39 ± 0.23	[31]
Imidazole, a-axis	^{14}C, ^{3}H	80–90	$10^{2.5 \pm 6}$	60 ± 10	[32]
γ-Iron	^{63}Ni	1130–1380	$0.44^{+0.3}_{-0.2}$	66.6 ± 1.6	[33]
AgCl	^{22}Na	180–300	8.81	27.4	[34]

Results for other monocrystalline substances can be obtained in a similar manner. Some examples are given in Table 1. The accuracy of the results naturally depends on the experimental conditions. Values for the diffusion of trace elements in single crystals, *e. g.* the diffusion of Ni in γ-Fe[33] or of Na in AgCl[34], can be treated in a similar manner.

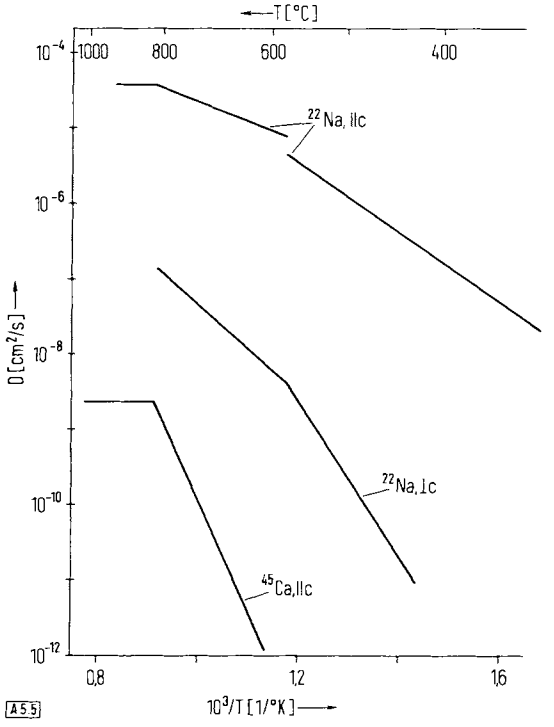


Fig. 5. Temperature dependence of the diffusion of traces of ^{22}Na and ^{45}Ca in quartz single crystals (cf. also Table 2) [35].

Table 2. Diffusion of traces of sodium and calcium in quartz single crystals [35]. D_0 = frequency factor, Q = activation energy.

Type	Temp. range [°C]	D_0 [cm²/s]	Q [kcal/mol]
∥ c, ^{22}Na	300–570	0.68 ± 0.12	20.2 ± 0.3
∥ c, ^{22}Na	600–800	$(7.09 \pm 1.06) \cdot 10^{-3}$	11.5 ± 0.2
⊥c, ^{22}Na	440–570	$(2 \pm 1) \cdot 10^2$	41 ± 1
⊥c, ^{22}Na	600–790	$(4 \pm 2) \cdot 10^{-2}$	27 ± 1
∥ c, ^{45}Ca	600–800	$(1 \pm 0.8) \cdot 10^5$	68 ± 2

The results for the diffusion of Na and of Ca in quartz single crystals reflect special properties of the substance investigated, *e. g.* the α-β transition at 573 °C, the strong anisotropy, and the temperature independence of the diffusion for $T > 800$ °C (cf. Table 2 and Fig. 5[35]). Measurements of this type can therefore be used for the structural characterization of the substances investigated.

4.1.2. Bicrystals and Polycrystals

4.1.2.1. General

The step from a single crystal to a polycrystalline material yields additional energetically favored sites at grain boundaries and other lattice defects. In the general case, therefore, one must expect a superposition of all possible components. If one first considers the coexistence of two processes, *e. g.* volume diffusion and grain-boundary diffusion, whose temperature dependences are described by Arrhenius functions of the type in eq. (9), the following relation is found for a combination of the two processes:

$$D_V/D_K = \text{const.} \exp[-(Q_V - Q_K)/RT] \quad (10)$$

D_V and D_K = diffusion coefficients for volume diffusion and for grain-boundary diffusion respectively [cm²/s]; Q_V and Q_K = activation energies of the corresponding processes [kcal/mol]

Since Q_V is always greater than Q_K, volume diffusion is always favored at higher temperatures, while grain-boundary diffusion is favored at lower temperatures.

According to *Harrison*[36], every diffusion process in a real solid with one-dimensional or two-dimensional crystal imperfections (dislocations or grain boundaries) passes through three successive stages, for which calculation is possible:

1. The mean depth of penetration in the volume is negligible, *i. e.*:

$$2\sqrt{D_V \cdot t} \ll \delta \quad (11)$$

δ = width of the lattice defects [cm]

2. $2\sqrt{D_V \cdot t}$ is large in relation to δ, but is nevertheless always smaller than the mean distance l [cm] between the lattice defects; the relation (12) is therefore valid (see Section 4.1.2.2):

$$2\sqrt{D_V \cdot t} < l \quad (12)$$

3. The mean depth of penetration in the volume is given by the relation (13) (see Section 4.1.2.3);

$$2\sqrt{D_V \cdot t} \gg \text{or at least} > l \quad (13)$$

The relation (11) can only be used for short diffusion times t. This case will therefore not be considered further.

4.1.2.2. Large Crystallites

Diffusion in large crystallites is represented by the model of a bicrystal with a two-dimensional, semi-infinite grain boundary of thickness δ (cf. Fig. 6), which was first proposed by *Fisher*[37].

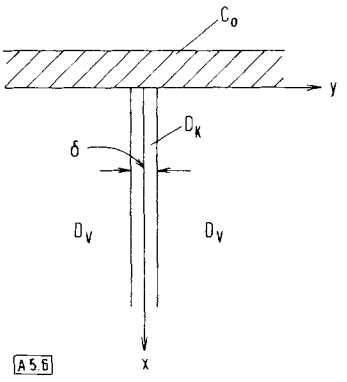


Fig. 6. Fisher model for the calculation of grain-boundary diffusion in bicrystals and polycrystals with large crystallites [37]. For explanation of the symbols, see text.

Diffusion equations must be set up both for the edge of the grain boundary and for the crystal outside the boundary, suitable continuity conditions being taken into account. The concentration within the grain boundary is of no interest, since the grain boundary is normally very narrow. Under the conditions specified by *Fischer*[37] (*i. e.* 1. initial condition corresponding to eq. (5); 2. constancy of δ; 3. $D_K \gg D_V$; and 4. perpendicular diffusion from the boundary into the grain), the following equation is found for the diffusion in the interior of the semi-infinite bicrystal [see also eq. (6)]:

$$c(x,y,t) = C_0 \exp(-\gamma x)\left[1 - \operatorname{erf}\left(\frac{y}{2\sqrt{D_V \cdot t}}\right)\right] \qquad (14)$$

where $\gamma = \sqrt[4]{\frac{4D_V}{\pi t}} \cdot \frac{1}{\sqrt{\delta \cdot D_K}}$

y = coordinate [cm]

If the mean grain size is greater than the maximum depth of penetration as a result of volume diffusion, one can integrate with respect to y, and the quantity that has diffused into a layer of thickness Δx is found to be

$$\bar{c}(x,t) = 4C_0 \sqrt{\frac{D_V \cdot t}{\pi}} \exp(-\gamma x) \qquad (15)$$

If the diffusion is followed by the serial sectioning method (cf. Section 3), γ (and hence the product $\delta \cdot D_K$) can be determined from the slope of the straight line $\log \bar{c}(x,t) = f(x)$ if D_V is known. *Hässner* and *Bergner*[38] were able to show that this simple relation is still valid when the residual activity is measured (see also Fig. 9).

These criteria have been substantially confirmed for many metallic bicrystals or polycrystals with large crystallites, *e.g.* for self-diffusion in Sn[39], γ-Fe[40], Ag[41], and Ni[33], and also for the diffusion of trace elements, *e.g.* of ^{63}Ni in γ-Fe[33]. Figure 7 shows an example of the diffusion of a ^{113}Sn/^{123}Sn mixture in polycrystalline tin having a purity of 99.99%[39]. The linearity demanded by eq. (15) is satisfied over a wide activity range; deviations due to superposition of a volume diffusion component occur only near the surface of the sample.

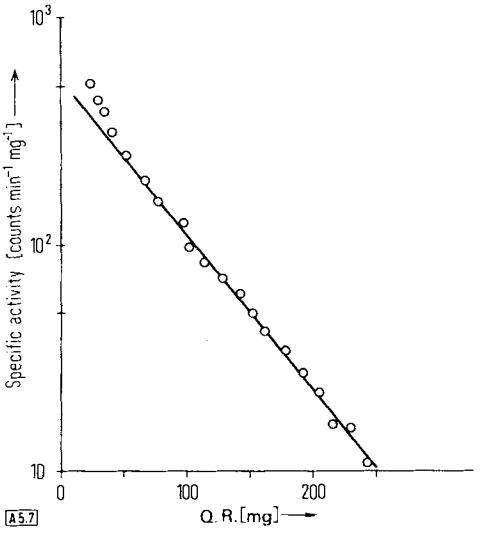


Fig. 7. Profile of the grain-boundary diffusion of ^{113}Sn/^{123}Sn in polycrystalline Sn, $T = 90$ °C, $t = 189$ h [39]. Q.R. = quantity removed. The diffusion coefficient is found to be $D_K = 1.11 \cdot 10^{-7}$ cm^2/s.

To be able to evaluate this diffusion profile for D_K, it is necessary to know D_V and δ, the width of the lattice defects. D_V has been measured between 150 and 225 °C[42] (cf. Table 3). Values for lower temperatures can be obtained from these results by extrapolation. *Fisher*[37] and many later authors (see *e.g.* in Ref. [39]) used a value of δ = 5 Å for metals. The profile shown in Figure 7 for D_K can be evaluated in this way. The temperature dependence of D_K can also be determined; in the case of Sn, one obtains $D_{0K} = (6.44^{+5.9}_{-4.9}) \cdot 10^{-2}$ cm^2/s and $Q_K = 9.55 \pm 0.70$ kcal/mol for the range from 39 to 115 °C. The autoradiogram reproduced in Figure 8 shows that the diffusion is in fact mainly grain-boundary diffusion. The blackening is essentially confined to the grain boundaries.

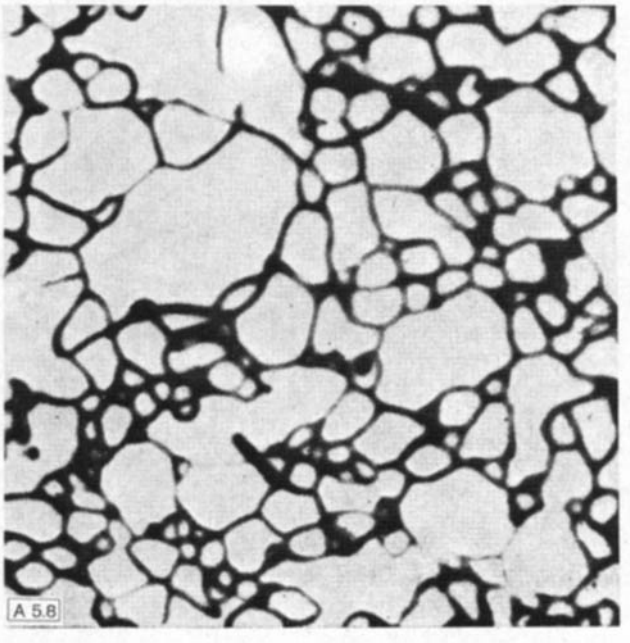


Fig. 8. Autoradiogram of a diffusion sample corresponding to Figure 7 [39], enlarged 15 times.

Table 3 contains other examples. Thus because of the imprecise knowledge of δ for the self-diffusion of Fe in γ-iron, *Lacombe et al.*[40] give only the value of $\delta \cdot D_{0K}$. The self-diffusion of

Table 3. Examples of the relation between volume diffusion, grain boundary diffusion, and dislocation diffusion in metals. D_0 = frequency factor, Q = activation energy.

Substance	Isotope	Temp. range [°C]	D_0 [cm²/s]	Q [kcal/mol]	Type	Ref.
Tin	$^{113}Sn/^{123}Sn$	150–225	$0.78^{+0.54}_{-0.32}$	22.8 ± 0.5	volume	[42]
Tin	$^{113}Sn/^{123}Sn$	39–125	$(6.44^{+5.9}_{-4.9})\cdot10^{-2}$	9.55 ± 0.70	grain boundary	[39]
γ-Iron	^{59}Fe	918–1259	0.58	67.9	volume	[40]
γ-Iron	^{59}Fe	918–1014	$1\cdot10^{7}$ [a]	40.0	grain boundary	[40]
Nickel	^{63}Ni	1149–1390	$1.39^{+0.9}_{-0.6}$	65.9 ± 1.5	volume	[33]
Nickel	^{63}Ni	850–1100	$(1.75^{+2.0}_{-1.0})\cdot10^{-2}$	28.2 ± 2.0	grain boundary	[33]
Nickel	^{63}Ni	500–600	20	36.9	grain boundary	[43]
γ-Iron	^{63}Ni	1130–1380	$0.44^{+0.3}_{-0.2}$	66.6 ± 1.6	volume	[33]
γ-Iron	^{63}Ni	940–1130	$(7.7^{+4.9}_{-2.6})\cdot10^{-1}$	36.4 ± 1.1	grain boundary	[33]

[a] $\delta\cdot D_{0K}$ in cm³/s

Ni has been studied in volume, along grain boundaries[33], and under the influence of edge dislocations[43] (plastic deformation of Ni single crystals). The diffusion of trace elements in metals, *e.g.* that of ^{63}Ni in γ-Fe, also falls in this category[33]. These examples show that diffusion is strongly accelerated by higher-dimensional lattice defects. As a rough rule, $Q_V/Q_K \approx 2$; a similar ratio is found for dislocation diffusion.

Grain-boundary diffusion also occurs in nonmetals. Some examples are the diffusion of ^{137}Cs in ice[44], of ^{36}Cl and ^{131}I in KCl and KI crystals[45], of ^{22}Na and ^{45}Ca in $Na_2O\cdot2CaO\cdot3SiO_2$[46], and of ^{22}Na in Al_2O_3[47]. *Zaplatynsky*[48] pointed out, however, that for many oxides or halides the ratio D_K/D_V is not of the order of 10^5, as in metals, but is close to 1. This can lead to difficulties in the evaluation based on the Fisher model[37], since one of the conditions for this model is $D_K \gg D_V$.

Curve 1 in Figure 9 shows an example of the diffusion of ^{22}Na in polycrystalline Al_2O_3 having a mean crystallite size of 23 μm[47]. Since the condition $D_K/D_V \gg 1$ is obviously satisfied in this case, the profile can be described according to

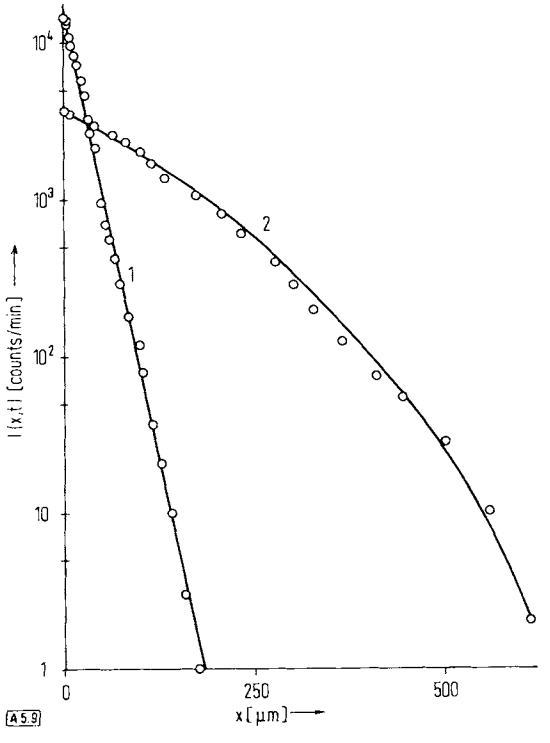


Fig. 9. Profile of the diffusion of ^{22}Na in polycrystalline Al_2O_3. Curve 1: T = 1223 °C, t = 2 h; Curve 2: T = 1750 °C, t = 0.75 h [47]. Plotted as residual activity I; x = thickness of removed layer. The diffusion coefficient is found from Curve 2 to be $D_{eff} = (6.24 \pm 1.20)\cdot10^{-8}$ cm²/s.

eq. (15) over the entire range. However, greater difficulties are encountered in the evaluation of such experiments for ionic crystals than for metals. This is because the effective width of the grain boundaries in ionic crystals is very strongly dependent on the impurities deposited at these boundaries (nature, quantity, valency). Unlike in the case of metals, long-range electric forces must be expected with excess atoms. It is not surprising, therefore, that *e.g.* in the diffusion of MgO, values of a few μm were found for the disturbed zone in the vicinity of grain boundaries[49]. However, if the crystals are extremely pure or if the impurities are distributed in the crystal rather than in the grain boundaries as a result of special heat treatment, the grain-boundary diffusion component (*i.e.* the effective disturbed zone) is much smaller[50].

The diffusion is again strongly dependent on the dislocation density in ionic crystals. As in the case of metals, the different dislocation densities were produced by plastic deformation of single crystals. A dislocation density of up to $3\cdot10^7$ cm/cm³ is obtained by this means in $SrTiO_3$ crystals. ^{18}O diffusion studies[51] show that when the dislocation density is changed by a factor of 2, the D_0 values change from $1.6\cdot10^{-7}$ to $1.2\cdot10^{-5}$ cm²/s, and the Q values change from 15.5 ± 2.0 to 29.3 ± 3.0 kcal/mol. In the diffusion of ^{90}Sr in $SrTiO_3$, the product $(\delta\cdot D_{disloc.})$ can be represented as a function of the dislocation density at 1875 °C by

$$(\delta\cdot D_{disloc.})_{Sr^{2+}} = 3.84\times10^{-19}\cdot\rho^{(0.23\pm0.10)}$$

and the corresponding ratio for ^{44}Ti can be represented[52] by

$$(\delta\cdot D_{disloc.})_{Ti^{4+}} = 2.92\times10^{-19}\cdot\rho^{(0.26\pm0.10)}$$

However, investigations of this type are still very inaccurate. The equations (14) and (15) calculated by *Fisher*[37] are merely approximate solutions. Later publications by *Whipple*[53], *Suzuoka*[54], *Levine* and *MacCallum*[55], and others give mathematically exact solutions for the case of an initial concentration in the form of a step or in the form of a point. *Le Claire*[56] and others found, however, that on the one hand the different initial conditions have only a small influence on the results, while on the other, in the relation

$$\log\bar{c}(x,t) = f(x^m)$$

in which $m = 1$ according to *Fisher*[37], other authors obtained $m = 4/3$[53], $6/5$[54], *etc.*, *i.e.* exponents that are very difficult to distinguish from 1 in this type of experiment.

Examples of the application of these more accurate calculation methods are to be found for the self-diffusion of Cl and I in KCl and KI respectively[57], of Sb in Sb metal[58], of Ti in α-Ti[59] and of Fe in Co[60].

4.1.2.3. Small Crystallites

The relation (13) is normally valid only for long diffusion times and small crystallites. The diffusing particle comes into contact with a very large number of crystal defects in succession as it passes through the crystal (cf. Fig. 10). Because of the frequent change between the possible sites, an effective mean diffusion process containing components of all kinds takes place. An experiment under these conditions should therefore give a diffusion profile similar to that in a single crystal, but with D_V in equations (4) and (6) replaced by D_{eff}. Curve 2 in Figure 9 shows an example of the diffusion of ^{22}Na in α-Al_2O_3[47]. The diffusion coefficient found here is the effective coefficient.



Fig. 10. Model for the occurrence of an effective diffusion process in a polycrystal with small crystallites.

Since grain-boundary diffusion is an effect of the internal surface, its influence should increase with decreasing crystallite size (*i.e.* with increasing surface area of the crystallites in relation to the volume). Measurements by *Laurent* and *Bénard*[45] on alkali metal halides with mean crystallite sizes of between 3000 and 30 μm showed the expected effect only for the (large and hence more strongly polarizable) ions Cs^+, Cl^-, Br^-, and I^-; the results for the ions Na^+ and K^+, on the other hand, agreed with those for single crystals. However, there have even been cases in which reversed dependence on the crystallite size was found[61]. Moreover, the influence of impurities is not yet clear.

Interesting approaches to the calculation of the effective diffusion in a real metallic solid have been described by *Hart*[62] and in particular by *Hässner*[63]. This model crystal is assumed to contain a sufficiently dense three-dimensional arrangement of lattice defects (grain boundaries, dislocations, pores), *i.e.* the relations (16) should be valid:

$$2\sqrt{D_V \cdot t} \gg l$$
$$2\sqrt{D_V \cdot t} \gg d \qquad (16)$$
$$2\sqrt{D_V \cdot t} \gg R_p \text{ or } d_p$$

l = crystallite diameter [cm]; d = distance between dislocations [cm]; R_p = pore radius [cm]; d_p = distance between pores [cm]

On the assumption that the model substance contains crystals in the form of cubes (width of grain boundary $\delta = 5 \cdot 10^{-8}$ cm), tubular dislocations with a radius $r_0 = 10^{-7}$ cm, and a relative pore volume of V_p/V, *Hässner*[63] found the following expression for the effective diffusion:

$$D_{eff} = \left(1 - \frac{3}{2}\frac{V_p}{V}\right) \cdot D_V + \frac{3}{2}\frac{\delta}{l} D_K + \pi \cdot 10^{-14} \rho \cdot D_p + \frac{3\delta'}{R_p} \cdot \frac{V_p}{V} D_0 \qquad (17)$$

δ' = thickness of the disturbed region of the internal surfaces [cm]; D_p = diffusion coefficient in the dislocations [cm^2/s]; D_0 = diffusion coefficient on the surface [cm^2/s]

$D_{0\,eff}$ and Q_{eff}, and hence the temperature dependence of the effective diffusion coefficient, can also be calculated on a similar basis.

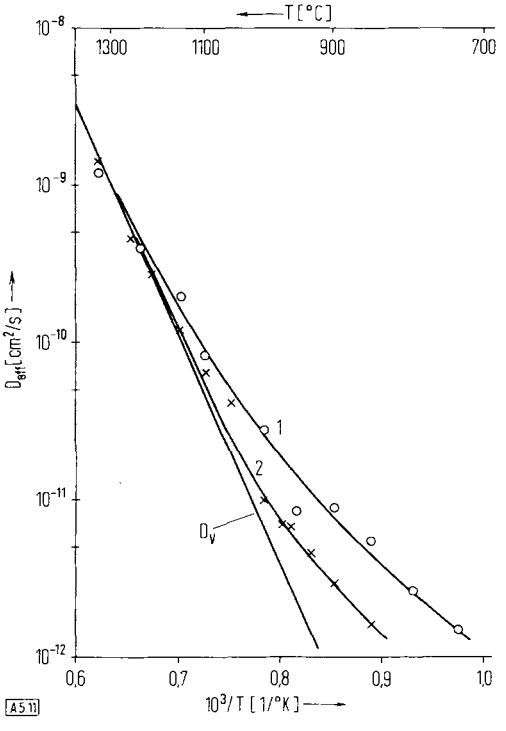


Fig. 11. Comparison of calculated and measured diffusion coefficients D_{eff} for sintered nickel. Series A (○): mean pore volume 8.2%, most frequent pore size 30 μm, most frequent grain size 33 μm; series B (×): mean pore volume 6.1%, most frequent pore size 10 μm, most frequent grain size 100 μm [64]. The Curves 1 and 2 for series A and B respectively were calculated from eq. (17).

Figure 11 shows the results of the experiments carried out by *Hässner et al.*[64] on sintered 99.7% pure nickel to verify these models. In addition to the temperature dependence of D_V (the volume self-diffusion measured on single crystals), Figure 11 shows experimental values for two series with different grain sizes and the corresponding calculated values. The agreement between calculation and experiment is good.

Several authors point out that the relations (16) and also (12) and (13) are sometimes very restrictive[36,63]. The derived models are approximately valid even when *e.g.* the relation $2\sqrt{D_V \cdot t} \approx l$ exists between the depth of penetration in the volume and the size of the lattice defects l. Definite transition states can also be evaluated experimentally. Thus *Lundy* and *Federer*[65] showed that for diffusion in UO_2, even in the

case of the Fisher model[37], a clear differentiation is possible between volume diffusion and grain-boundary diffusion in a concentration curve. The same is true of self-diffusion in tellurium[66] and of the self-diffusion of Na and Ca in $Na_2O \cdot 2CaO \cdot 3SiO_2$[46]. A check on the literature dealing with diffusion measurements on polycrystalline material often reveals deviations from the models, which are themselves clearly formulated.

4.1.3. Crystal Surfaces

The surfaces of solids naturally also provide energetically favored sites for the transport of matter. Experiments for the detection of such processes can be carried out *e.g.* with radioactive isotopes. However, transport on the surface can also be observed in sintering experiments, in the smoothing of surface scratches, *etc.* (for reviews see Refs. [67—69]).

4.1.4. Glasses

Glasses are characterized by the fact that their structure consists of a more or less disordered network. Though the ordering of the individual $SiO_{4/2}$ tetrahedra (if one regards silica glasses or silicate glasses as typical representatives of this class of substances) results in a short-range order, the long-range order typical of crystals is absent because of the different ways in which the individual tetrahedra are linked, *e.g.* to form

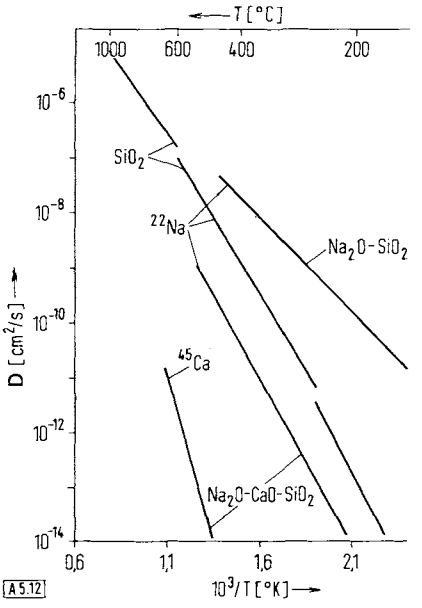


Fig. 12. Temperature dependence of the diffusion of ^{22}Na and ^{45}Ca in silicate glasses (cf. Table 4) [70, 72].

five-membered, six-membered, seven-membered, and larger rings, and because of other types of disorder. A higher degree of order may be produced in certain regions by phase separation processes, but these structures still resemble those of liquids rather than of crystals.

Self-diffusion experiments on a homogeneous glass (*e. g.* with ^{22}Na on a glass from the $Na_2O—SiO_2$ system) lead to the initially surprising result that the diffusion profiles, as in the case of ideal single crystals, can be described by unequivocal values of the diffusion coefficient over the entire activity range. Despite the ill-defined structure of the glass, the sites available to the migrating particles must be structurally and energetically equivalent[70]. Deviations from this simple behavior occur only in special cases, *e. g.* when, as a result of phase separation, the glass has a structure in which clearly different diffusion sites have been produced[71].

Figure 12 shows some typical diffusion results for glasses; the corresponding D_0 and Q values are shown in Table 4. The Na ion is much more mobile in binary $Na_2O—SiO_2$ glasses than in ternary $Na_2O—CaO—SiO_2$ glasses. Silica glass with trace contents in the ppm range assumes an intermediate position in this respect. It can also be seen from Figure 12 that the doubly charged Ca^{2+} ions have a much lower diffusion coefficient and a much higher activation energy than the Na^+ ions in the same ternary glass (for further results on the self-diffusion of other ions or in other glasses, see *e. g.* in Refs. [24-26, 70, 72]).

Table 4. Examples of self-diffusion in glasses [70, 72]. D_0 = frequency factor, Q = activation energy.

Glass	Isotope	Temp. range [°C]	D_0 [cm²/s]	Q [kcal/mol]
SiO_2 [a]	^{22}Na	170–250	2.13 ± 0.29	28.3 ± 0.2
SiO_2 [a]	^{22}Na	250–600	0.374 ± 0.019	25.8 ± 0.1
SiO_2 [a]	^{22}Na	600–1000	$(4.05 \pm 0.24) \cdot 10^{-2}$	21.6 ± 0.1
$Na_2O—SiO_2$	^{22}Na	100–400	$(2.46 \pm 0.13) \cdot 10^{-3}$	15.7 ± 0.1
$Na_2O—CaO—SiO_2$	^{22}Na	200–600	$(3.76 \pm 0.47) \cdot 10^{-2}$	27.3 ± 0.2
$Na_2O—CaO—SiO_2$	^{45}Ca	470–600	$(3.39 \pm 0.49) \cdot 10^{2}$	56.2 ± 0.3

[a] Silica glass with traces of Na.

4.2. Chemical Diffusion

In chemical diffusion, the diffusion partners differ in their chemical composition. Figure 3 showed a concentration curve in the binary system $MgO—Fe_2O_3$. The values obtained by the Boltzmann-Matano evaluation[9, 10] (cf. Section 2) were a little too high, since the molar volume of the spinel phase formed is different from that of MgO. On the other hand, if the curve is evaluated by *Wagner's* method[11], the results in Figure 13 are obtained for D_{Fe}[18]. The diffusion coefficient thus shows a very distinct dependence on the Fe concentration in the substance. The changes in the activation energy (between 49 and 80 kcal/mol) are attributed to the variation of the ratio $Fe^{2+}/Fe_{tot.}$ with the temperature, the oxygen partial pressure, and the total iron content.

The diffusion behavior of two metals that have been brought into contact is shown schematically in Figure 14. Since the two components have different mobilities, different diffusion fluxes occur in the two directions. For each jump of an atom,

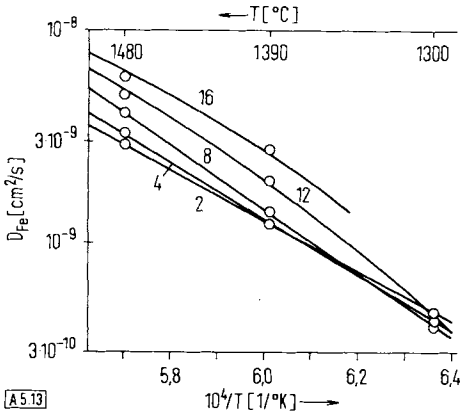


Fig. 13. Temperature dependence of $D_{Fe^{3+}}$ in the binary system $MgO—Fe_2O_3$ [18]. The figures by the curves indicate the Fe content [%].

there is a corresponding migration of a vacancy in the opposite direction. The result is that the vacancies heal in one sample, *i.e.* the sample becomes shorter and possibly thinner, while in the other sample new vacancies are formed, *i.e.* this sample becomes longer and possibly thicker. The changes in the dimensions are manifested in particular in a displacement of the original separation plane and in the formation of a swelling on one side and a constriction on the other, often accompanied by a zone containing holes. This is a zone in which vacancies have united instead of reaching equilibrium with the lattice. This phenomenon is also known as the Kirkendall effect[73] (for further information see *e.g.* in Ref. [74]).

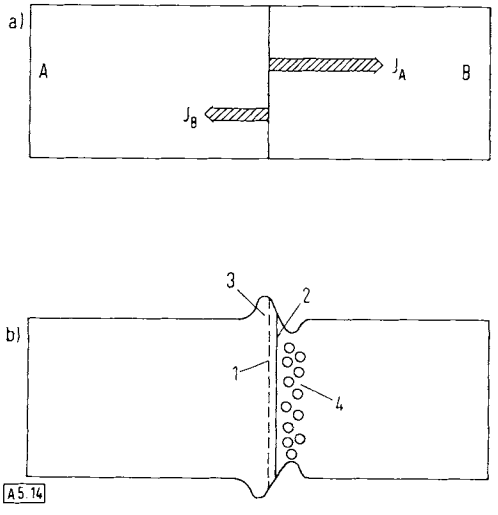


Fig. 14. Diagram illustrating the Kirkendall effect [73]. a) Representation of the mass fluxes J_A and J_B; b) appearance after diffusion; 1 and 2 = welding plane before and after the experiment respectively, 3 = swelling, 4 = holes.

Chemical diffusion in glasses occurs when *e.g.* a solid glass containing Na is introduced into a salt melt containing K and the surface of the glass is modified as a result of an exchange reaction of the type:

$$(Na^+)_{glass} + (K^+)_{melt} \rightleftarrows (Na^+)_{melt} + (K^+)_{glass} \qquad (18)$$

By measurement of the Na and K concentrations in the glass with a microprobe, it can be shown that the Na:K exchange actually occurs in a ratio of 1:1, and that the remainder of the glass structure (consisting *e.g.* of Si, O, Al) is unaffected.

Curve 1 in Figure 15 shows the K—Na interdiffusion coefficient $\tilde{D}$[*] obtained according to Boltzmann-Matano[9,10] as a function of the equivalent fraction of the K^+ ions $N_K = c_K/(c_K + c_{Na})$.

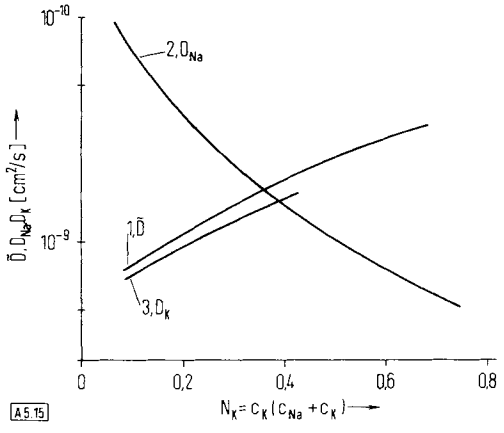


Fig. 15. Relation between chemical diffusion and self-diffusion in glasses. Curve 1: measured interdiffusion coefficient D; Curve 2: measured self-diffusion coefficient D_{Na}; Curve 3: self-diffusion coefficient D_K calculated from eq. (23) [77]. $T = 400$ °C.

If two cations with different mobilities interdiffuse in a rigid network of anionic groups, an electric potential is produced in order to maintain equal ion fluxes, and hence electroneutrality. The flux J_i of the ionic species i in the x direction can be described by the Nernst-Planck equations[75]

$$J_i = \frac{u_i}{F}\left(RT\frac{\partial c_i}{\partial x}\cdot\frac{\partial \ln a_i}{\partial \ln c_i} + z_i c_i F E\right) \qquad (19)$$

u = electrochemical mobility [cm²/Vs]; z = valency; a = thermodynamic activity [g/cm³]; F = Faraday constant [C/mol]; E = electric field strength [V/cm]

From these equations and the condition for electroneutrality, one obtains

$$J_A = -\tilde{D}\cdot\frac{\partial c_A}{\partial x} \quad \text{and} \quad J_B = -\tilde{D}\cdot\frac{\partial c_B}{\partial x} \qquad (20)$$

with the interdiffusion coefficient

$$\tilde{D} = \frac{D_A \cdot D_B}{N_A D_A + N_B D_B}\cdot\frac{\partial \ln a_A}{\partial \ln c_A} \qquad (21)$$

with $N_i = c_i/(c_A + c_B)$, the molar content of the ionic species i. Only for the case of an ideal solution, *i.e.* for $\partial \ln a/\partial \ln c = 1$, does one obtain the generally known form

$$\tilde{D} = \frac{D_A \cdot D_B}{N_A D_A + N_B D_B} \qquad (22)$$

D_A and D_B = self-diffusion coefficients of A and B respectively [cm²/s]

These arguments will now be applied to the example shown in Figure 15. Curve 1 shows the measured interdiffusion coefficient, curve 2 shows the course of the self-diffusion coefficients

[*] "Interdiffusion" is the name given to the special case of binary alkali metal ion exchange with a stable SiO network.

D_{Na}[76], and the course of the self-diffusion coefficient D_K in this system can be calculated from

$$\tilde{D}_K = \frac{\tilde{D} \cdot D_{Na}(1 - N_K)}{D_{Na} - \tilde{D} N_K} \tag{23}$$

(cf. curve 3)[77].

An interesting technical application of ion exchange processes of this type will be briefly mentioned here. If this process is carried out at a temperature that is far enough below the transformation temperature T_g of the glass (*i.e.* the glass structure should be perfectly rigid), the exchange of the smaller Na^+ ion for the much larger K^+ ion (0.96 and 1.33 Å respectively) results in high compressive stresses (up to 7000 kp/cm^2) in the affected surface layer. The stresses are retained only while the structure is rigid. This procedure ("chemical strengthening of glasses") is being used to an increasing extent to increase the strength of glass objects[78, 79].

Investigations on chemical diffusion in ternary systems are much more complicated. No general conclusions can be drawn at present (cf. *e.g.* investigations on the systems MgO—Fe_2O_3—Ce_2O_3[18] and Fe—Si—C[80] and on glasses of the K_2O—SrO—SiO_2 system[81]).

5. Diffusion Mechanisms

5.1. Correlation Effects

Though only one particle in 10^3 to 10^4 is incorrectly arranged in single crystals even close to the melting point[82], this imperfection is of decisive importance to mass transport. Figure 16 illustrates four of the possible diffusion mechanisms for a monatomic crystal. A direct exchange of places between adjacent particles is energetically improbable, particularly in the case of ionic compounds (Fig. 16a). In the direct interstitial mechanism (Fig. 16b) a particle in the interstitial space continues to move in this space, while in the vacancy mechanism (Fig. 16c) a sufficient number of unoccupied positions must

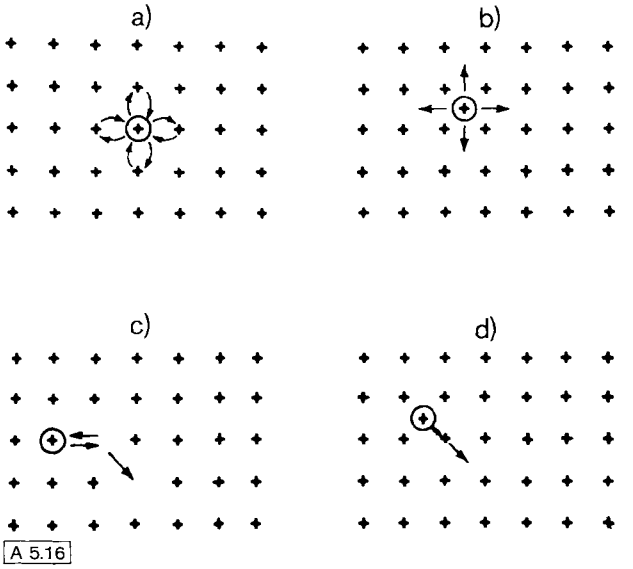


Fig. 16. Diagrams of several possible diffusion mechanisms in a monoatomic crystal. a) Direct exchange mechanism, $f = 1$; b) direct interstitial mechanism, $f = 1$; c) vacancy mechanism, $f = 0$—1; d) interstitialcy mechanism, $f = 0$—1. f = correlation factor (see eq. (24) and Table 5).

be available; in the indirect interstitial mechanism (interstitialcy mechanism) (Fig. 16d), a particle in an interstitial site pushes a particle from the lattice into an interstitial site and occupies the lattice site for itself. All these elementary steps require a particular "threshold energy" U (migration energy), which corresponds to the saddle point of the migrating particle between the initial and final states (cf. Fig. 17).

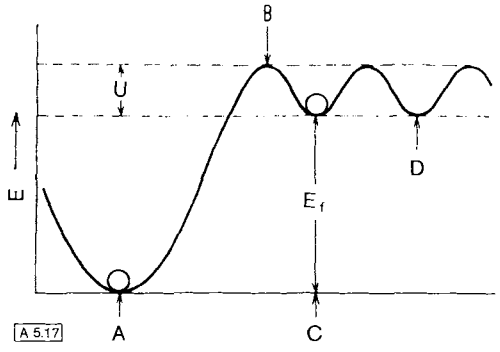


Fig. 17. Potential energy diagram for a particle in various lattice positions. A = occupied normal lattice site, B = saddle point for transfer into interstitial site, C = occupied interstitial site, D = unoccupied interstitial site, E_f = energy of defect formation, U = threshold energy.

Both in the exchange mechanism and in the direct interstitial mechanism, diffusing radioactive particles can execute steps in all directions with equal probability if the substance in which the diffusion occurs is isotropic. In the vacancy mechanism and in the interstitialcy mechanism, on the other hand, all the successive steps of a particle are no longer equally probable. A particle (cf. Fig. 16c) migrates *e. g.* into a vacancy. However, the next step of this particle will be in the forward direction only if a suitable vacancy is again available. In any case there is always a vacancy behind the particle, *i.e.* the vacancy created by the particle itself as it migrated. The same is true of the interstitialcy mechanism (Fig. 16d). Successive steps are therefore no longer independent of one another, and one speaks of a correlation effect of self-diffusion. The correlation factor f describing this effect can be derived from a series expansion from the general diffusion equation, and is found[83, 84] to be as follows:

$$f = 1 + 2\cos\vartheta_1 + 2\cos\vartheta_2 + \cdots \tag{24}$$

ϑ_i = angle between the i-th and the (i+j)-th steps

f can assume values between 0 and 1, depends on the geometry of the lattice and on the diffusion mechanism, and can be calculated from theoretical arguments (cf. Table 5)[85].

Table 5. Calculated correlation factors f for diffusion by a vacancy mechanism (V) and by an interstitialcy mechanism (I) [85].

V		I	
Lattice type	f	Lattice type	f
Diamond	0.5000	AgCl	0.3333
Cubic	0.6531	CaF_2	0.4
Cubic body centered	0.7272	$CdCl_2$	$f_x = f_z = 0.4$
Cubic face centered	0.7815		
Hexagonal close packing	$f_x = f_y = 0.7812$; $f_z = 0.7815$		

5.1.1. Conductivity Methods

There are two methods for the experimental determination of f. The first method can be used only for ionic crystals. According to Nernst-Einstein, the tracer diffusion of the corresponding ionic species and the specific electrical conductivity are related as follows:

$$D_i^* = \frac{\sigma \cdot s_i \cdot k \cdot T}{n_i (z_i e)^2} \cdot f_i \qquad (25)$$

D^* = tracer diffusion coefficient [cm^2/s]; σ = total specific electrical conductivity [$\Omega^{-1}\,cm^{-1}$]; s = transport number; k = Boltzmann's constant [J/°K]; n = number of ions/cm^3; z = valency; e = elementary charge [A.s]

These arguments were first checked on heavy metal halides such as AgBr and AgCl[30, 86-88]. The f values of between 0.4 and 0.6 found experimentally for Ag^+ agree with the calculated values if one assumes an interstitialcy mechanism proceeding in the cation sublattice. This also agrees with the fact that the cation sublattice in heavy metal halides is imperfect because of Frenkel defects. More recent investigations on AgCl suggest that there may even be two slightly different interstitialcy mechanisms for the Ag^+ ions (collinear and noncollinear steps of the two particles involved)[89].

However, if bivalent ions are incorporated into the lattice (*e. g.* $CdBr_2$ into AgBr single crystals), the number of Ag interstitial sites decreases at the cost of the Ag vacancies; the f value of 0.80 that is then found clearly points to a vacancy mechanism. A similar situation was found for $CdBr_2$-doped AgCl crystals, with $f = 0.78$[90].

These arguments have also been applied to glasses, which resemble heavy metal halides, in these respects[91, 70]. Experimental f values of about 0.4 to 0.5 again point to an interstitialcy mechanism, but it must be remembered here that lack of knowledge about the structure of glass introduces an unknown into these considerations.

5.1.2. Isotope Effect Method

The second method for the experimental determination of f involves the measurement of the isotope effect of the self-diffusion by the use of different isotopes of the same element[84]. Since the heavier particle is naturally slower, one obtains eq. (26) on the assumption that not more than one building unit jumps in the mechanism under consideration[*]:

$$f \cdot \Delta K = \frac{1 - D_2/D_1}{1 - \sqrt{m_1/m_2}} \qquad (26)$$

m_1, m_2 = masses of the diffusing particles [g], $\Delta K \leq 1$

Unlike the conductivity method, this method for the determination of f is not confined to ionic compounds. It can be used whenever two suitable isotopes of the same element exist, *e. g.* ^{22}Na and ^{24}Na, ^{55}Fe and ^{59}Fe, ^{55}Co and ^{60}Co, ^{65}Zn and ^{69}Zn, ^{103}Pd and ^{112}Pd, ^{105}Ag and ^{110}Ag, *etc.* Thus vacancy mechanisms have been found in this way *e. g.* for NaCl[84], for Pd[15] and for CoO[31], in agreement with other considerations, according to which vacancy processes should predominate for alkali metal halides, for close-packed metals, and for most oxides.

On the other hand, as in the consideration of the correlation effect, it must be concluded from the isotope effect of $^{105}Ag/^{110}Ag$ in the heavy metal halide AgBr[92] that an interstitialcy mechanism operates here. The $^{22}Na/^{24}Na$ isotope effect has recently also been determined for a glass from the Na_2O—SiO_2 system[93]. Here again, in comparison with the behavior of the Ag^+ ion in AgBr, it is found that the Na^+ ion must be subject to an interstitialcy mechanism. The values found experimentally are shown in Table 6.

Table 6. Results of some isotope effect measurements. f = correlation factor, $\Delta K \leq 1$.

Substance	Isotopes	$f \cdot \Delta K$	Mechanism	Ref.
NaCl	^{22}Na, ^{24}Na	0.78	vacancy mechanism	[84]
Pd	^{103}Pd, ^{112}Pd	0.8134 ± 0.0424	vacancy mechanism	[15]
CoO	^{55}Co, ^{60}Co	0.582 ± 0.009	vacancy mechanism	[31]
AgBr	^{105}Ag, ^{110}Ag	0.29	collinear interstitialcy mechanism	[92]
Na_2O—SiO_2-glass with 17.4 mol-% Na_2O	^{22}Na, ^{24}Na	0.25	similar as in AgBr	[93]

5.2. Thermodynamic-Statistical Considerations

5.2.1. Activation Energy and Frequency Factor

If the diffusion coefficient is determined as a function of the temperature, the characteristic values D_0 (frequency factor) and Q (activation energy) can be determined from the initially empirical Arrhenius equation (9). What do these parameters tell us?

To find the answer, let us again consider Figure 17. For a diffusion step, an arbitrarily selected particle requires the threshold energy U in addition to the defect energy E_f. The activation energy found experimentally thus normally contains two components; in particular, $Q = E_f + U$ for a monatomic substance with Schottky defects and $E_f/2 + U$ for an ionic compound of the type A^+B^-. However, the separate experimental determination of the two energy components is possible only in special cases, in ionic crystals *e. g.* with the aid of electrical conductivity results[82]. This applies *e. g.* to the migration energy if a "frozen" disorder is present or if the substance contains practically no thermally activated defects below a certain temperature. For this extrinsic range $E_f \approx 0$ and hence $Q \approx U$.

[*] If several particles take part, *e. g.* in the interstitialcy mechanism, eq. (26) must be replaced by a rather more complicated formula.

The migration energy U and the vibration frequency $\nu[s^{-1}]$ of the particles in the potential well are related as follows

$$\nu = \frac{1}{2b}\sqrt{U/2m} \tag{27}$$

b = distance of jump [cm]; m = mass of the particle [g]

on the assumption of a sine-shaped diffusion potential that is approximated close to the equilibrium position by a second order parabola. The vibration frequency should be close to ν_D (Debye frequency). A number of comparisons carried out so far show satisfactory agreement in some cases between theory and experiment. Thus the calculated migration energy for rhombic PbO was 21.9—27.7 kcal/mol, while the Q value found from the diffusion was 22.4 kcal/mol[94].

A number of relations have been given for the frequency factor D_0; the following equation was proposed by *Zener*[95]:

$$D_0 = \gamma \cdot f \cdot \nu \cdot b^2 \exp(\Delta S/R) \tag{28}$$

γ = geometric factor; $(\Delta S/R)$ = diffusion entropy factor

ΔS can also be broken down into a component for the migration of the particle and a component for the formation of imperfections. D_0 has been calculated at least approximately for a number of metals with the aid of this or similar equations, and compared with experimental values (cf. Ref. [74]). However, difficulties generally arise in the calculation of the diffusion entropy

$$\Delta S = k \sum_i \ln(\nu_i/\nu_i') \tag{29}$$

since the vibration frequencies ν_i (undistorted lattice) and ν_i (distorted lattice) are unknown.

In most cases, therefore, the entropy has the character of a quantity to be adapted. A tendency has been found experimentally for a vacancy mechanism to exist when $(\Delta S/R) > 0$, and an interstitial mechanism when $(\Delta S/R) < 0$. The negative migration entropy may be due to local density increases in interstitial diffusion, which are associated with an increase in the vibration frequencies, since it follows for $\nu_i' > \nu_i$ that

$$\Delta S = k \sum_i \ln(\nu_i/\nu_i') < 0$$

It may also be of interest in this connection that estimates of this type for glasses give negative entropy factors[70]. This again supports the suggestion of an interstitial process.

All these considerations lead to the conclusion that diffusion in close-packed metals normally proceeds by a vacancy mechanism. Participation of interstitial sites cannot be ruled out in less closely packed semiconductor crystals. A vacancy mechanism also operates in the diffusion of cations in alkali metal halides and in a series of oxides; exceptions are found in the diffusion of anions *e.g.* in UO_2, NiO, and MgO. An interstitial mechanism predominates in these cases. This is to be expected in particular for substances having structures in which there are large interstitial spaces (*e.g.* because of a lamellar, chain, or sheet structure). It has also been established that the diffusion of cations in heavy metal halides takes place by an interstitialcy mechanism. There is evidence that this is also true of the diffusion of alkali metals in silicate glasses.

5.2.2. Influence of Divacancies

There have recently been growing signs that the diffusion in a series of substances cannot be described by a simple Arrhenius function corresponding to eq. (9) over the entire temperature range up to the melting point. The closer one comes to the melting point, the greater are the deviations. Satisfactorily verified values are available for the diffusion of Cl in NaCl[96], the diffusion of Na in AgCl[97], the self-diffusion of Ni[98] and Ag[99], and a number of other cases. All the authors explain these cases by the coexistence of two mechanisms. The normal course is described by a process involving single vacancies, and the abnormal course by a process involving divacancies. Since the two processes have different D_0 and Q values, the resulting function deviates from linearity in the Arrhenius diagram.

5.2.3. Knowledge of the Imperfection

Whereas our knowledge of the imperfection in halides, metals, and simple oxides is relatively good, very little is known about the situation in more complicated substances, *e.g.* the silicates[100]. Also the interpretation of chemical diffusion processes in binary and especially in ternary systems on the basis of imperfection models is still in its infancy[18,101]. The point on which the least is known is the nature of the "defect centers" in glasses, which have a highly distorted structure in any case. When Frenkel's view on the formation of a pair of defects is applied to a glass, the following dissociation process in the structure must be taken into account:

$$[SiO_{3/2}O^-M^+] + [SiO_{4/2}] \rightleftarrows [SiO_{3/2}O^-] + [M^+SiO_{4/2}] \tag{30}$$

The groups on the left-hand side are uncharged; the charged complexes on the right may be formally compared to a vacancy or an interstitial ion in a crystalline substance. The number of these "pairs of defects" can be calculated as a function of temperature in much the same way as *e.g.* for AgBr. According to this model, the measured activation energy Q should contain both formation and migration components.

On the other hand, if one uses a model suggested by *Charles*[102] for the glass structure, in which, because of the loose arrangement, the number of sites that can be occupied by alkali metal ions is greater than the number of alkali metal ions present, Q would merely contain an energy component for migration. According to the arguments of *Lengyel* and *Boksay*[103] this second possibility should exist in glasses.

6. Closing Remarks

One aim of this report was to show that both the experimental and the theoretical principles of mass transport by diffusion are largely independent of the nature of the solid investigated. The measuring procedures must naturally be matched to the material under consideration, and the discussion of the mechanism starts with the structure that is present and its

imperfection; in principle, however, the same questions arise for all materials, regardless of whether they are crystalline or noncrystalline substances, whether the solid is inorganic or organic, or whether the bonding in the substances is metallic, heteropolar, or of some other type.

A focal point for further investigations in the near future will be diffusion in multicomponent systems, both for phenomenological description and for explanation on the basis of imperfection models. Further investigations on the influence of dislocations and grain boundaries on mass transport are also necessary; importance should also be placed here on the question of the mechanism of such processes, since practically nothing is known about this field. Further results for noncrystalline substances would also be desirable; in the case of oxide glasses, the mobility of the particles forming the network (*e.g.* Si) is particularly interesting. Knowledge about diffusion in nonoxide glasses is also lacking at present. Investigations of this nature may also help to provide information about the structures that are not very amenable to direct methods (*e.g.* X-ray diffraction).

Another trend in these investigations will be the reliable measurement and interpretation of small deviations from normal behavior. Increases in measuring accuracy and better characterization of the substances may contribute in this connection.

As was mentioned in the introduction, diffusion also plays an important part in a number of technical processes. To obtain a better theoretical understanding of these processes, and hence to be able to make them more efficient, results from diffusion in solids should be applied in practice to a greater extent than in the past. Since the procedure in these fields is still often very empirical, knowledge about mass transport is not merely of academic interest.

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[1] *W. Jost*, Angew. Chem. *76*, 473 (1964); Angew. Chem. internat. Edit. *3*, 713 (1964).

[2] *W. Jost* and *K. Hauffe:* Diffusion. Methoden der Messung und Auswertung. 2. Edit. Steinkopff, Darmstadt 1972.

[3] *W. Jost:* Diffusion in Solids, Liquids, Gases. Academic Press, New York 1952.

[4] *J. Crank:* The Mathematics of Diffusion. Clarendon Press, Oxford 1957.

[5] *K. Hauffe:* Reaktionen in und an festen Stoffen. 2. Edit. Springer, Berlin 1966.

[6] *H. Schmalzried:* Festkörperreaktionen. Verlag Chemie, Weinheim 1971.

[7] *J. R. Manning:* Diffusion Kinetics for Atoms in Crystals. Van Nostrand, Princeton, N. J. 1968.

[8] *P. G. Shewmon:* Diffusion in Solids. McGraw-Hill, New York 1963.

[9] *L. Boltzmann*, Wied. Ann. *53*, 959 (1894).

[10] *C. Matano*, Jap. J. Phys. *8*, 109 (1933).

[11] *C. Wagner*, Acta Met. *17*, 99 (1969).

[12] *E. g. C. M. Lederer, J. M. Hollander*, and *I. Perlman:* Table of Isotopes. 6. Edit. Wiley, New York 1967.

[13] *W. Rupp, U. Ermert*, and *R. Sizmann*, Phys. Status Solidi *33*, 509 (1969).

[14] *G. H. Frischat* and *H. J. Oel*, Z. Angew. Phys. *20*, 195 (1966).

[15] *N. L. Peterson*, Phys. Rev. *136*, A 568 (1964).

[16] Cf. *R. Lindner*, Acta Chem. Scand. *5*, 735 (1951).

[17] *H. Malissa:* Elektronenstrahl-Mikroanalyse. Springer, Vienna—New York 1966.

[18] *W. Hering*, Ber. Deut. Keram. Ges. *48*, 67 (1971).

[19] *F. R. Winslow*, J. Metals *16*, 589 (1964).

[20] *P. A. Cumming* and *P. J. Harrop*, AERE-Report 1966.

[21] *G. L. de Poorter* and *T. C. Wallace*, Advan. High Temp. Chem. *4*, 107 (1971).

[22] *P. Süptitz* u. *J. Teltow*, Phys. Status Solidi *23*, 9 (1967).

[23] *A. L. Dragoo*, J. Res. Nat. Bur. Stand. *72 A*, 157 (1968).

[24] *G. H. Frischat*, Glas-Email-Keramo-Tech. *22*, 275 (1971); Glastech. Ber. *45*, 309 (1972).

[25] *R. H. Doremus* in *J. D. Mackenzie:* Modern Aspects of the Vitreous State. Vol. 2. Butterworths, London 1962; *K. K. Evstrop'ev:* Diffusionsprozesse im Glas. Literatur zum Aufbau, Leningrad 1970.

[26] *F. H. Wöhlbier:* Diffusion Data. Diffusion Information Center, Solothurn. Vol. 1—7, 1967—1973.

[27] *E. Hoinkis* and *H. W. Levi*, Z. Naturforsch. *22a*, 226 (1967).

[28] *W. P. Ellis* u. *N. H. Nachtrieb*, J. Appl. Phys. *40*, 472 (1969).

[29] *Yu. P. Maslakovets, E. N. Mokhov, Yu. A. Vodakov*, and *G. A. Lomakina*, Soviet Phys. Solid State *10*, 634 (1968).

[30] *W. D. Compton* u. *R. J. Maurer*, J. Phys. Chem. Solids *1*, 191 (1956).

[31] *W. K. Chen, N. L. Peterson*, and *O. Reeves*, Phys. Rev. *186*, 887 (1969).

[32] *A. R. McGhie, H. Blum*, and *M. M. Labes*, J. Chem. Phys. *52*, 6141 (1970).

[33] *W. Lange, A. Hässner*, and *G. Mischer*, Phys. Status Solidi *5*, 63 (1964).

[34] *P. Süptitz*, Phys. Status Solidi *12*, 555 (1965).

[35] *G. H. Frischat*, Phys. Status Solidi *35*, K 47 (1969); Ber. Deut. Keram. Ges. *47*, 238, 313, 364, 635 (1970); J. Amer. Ceram. Soc. *53*, 357 (1970).

[36] *L. G. Harrison*, Trans. Faraday Soc. *57*, 1191 (1961).

[37] *J. C. Fisher*, J. Appl. Phys. *22*, 74 (1951).

[38] *A. Hässner* and *D. Bergner*, Isotopentechnik *1*, 193 (1960/61).

[39] *W. Lange* and *D. Bergner*, Phys. Status Solidi *2*, 1410 (1962).

[40] *P. Lacombe, P. Guiraldenq*, and *C. Leymonie* in: Radioisotopes in the Physical Sciences and Industry. International Atomic Energy Agency, Vienna 1962, 179ff.

[41] *J. Kučera*, Czech. J. Phys. *B 14*, 915 (1964).

[42] *W. Lange, A. Hässner*, and *I. Berthold*, Phys. Status Solidi *1*, 50 (1961).

[43] *M. Wuttig* and *H. K. Birnbaum*, Phys. Rev. *147*, 495 (1966).

[44] *H. H. G. Jellinek* and *K. Juznic*, Phys. Status Solidi *A 2*, 837 (1970); *H. H. G. Jellinek* and *A. K. Chatterjee, ibid. A 4*, 173 (1971).

[45] *J. F. Laurent* and *J. Bénard*, C. R. Acad. Sci. *241*, 1204 (1955); J. Phys. Chem. Solids *7*, 218 (1958).

[46] *G. H. Frischat*, Z. Angew. Phys. *22*, 281 (1967); Ber. Deut. Keram. Ges. *44*, 232 (1967).

[47] *G. H. Frischat*, Ber. Deut. Keram. Ges. *48*, 441 (1971).

[48] *I. Zaplatynsky*, J. Appl. Phys. *35*, 1358 (1964).

[49] *B. J. Wuensch* and *T. Vasilos*, J. Amer. Ceram. Soc. *47*, 63 (1964).

[50] *B. J. Wuensch* and *T. Vasilos*, J. Amer. Ceram. Soc. *49*, 433 (1966).

[51] *A. E. Paladino, L. G. Rubin*, and *J. S. Waugh*, J. Phys. Chem. Solids *26*, 391 (1965).

[52] *W. H. Rhodes* and *W. D. Kingery*, J. Amer. Ceram. Soc. *49*, 521 (1966).

[53] *R. T. P. Whipple*, Phil. Mag. *45*, 1225 (1954).

[54] *T. Suzuoka*, J. Phys. Soc. Jap. *19*, 839 (1964).

[55] *H. S. Levine* and *C. J. MacCallum*, J. Appl. Phys. *31*, 595 (1960).

[56] *A. D. LeClaire*, Brit. J. Appl. Phys. *14*, 351 (1963).

[57] *J. Cabané*, J. Chim. Phys. Physicochim. Biol. *59*, 1123, 1135 (1962).

[58] *A. Hässner* and *G. Voigt*, Z. Metallk. *59*, 559 (1968).

[59] *C. M. Libanti* and *F. Dyment*, Acta Met. *11*, 1263 (1963).

[60] *M. Aucouturier, O. Pinheiro Ribeiro de Castro*, and *P. Lacombe*, Acta Met. *13*, 125 (1965).

[61] *G. H. Frischat*, Naturwissenschaften *53*, 610 (1966).

[62] *E. W. Hart*, Acta Met. *5*, 597 (1957).

[63] *A. Hässner*, Phys. Status Solidi *11*, K 15 (1965); Neue Hütte *12*, 161 (1967).

[64] *A. Hässner, L. Ehrhardt, G. Engelmann*, and *B. Epler*, Neue Hütte *12*, 286 (1967).

[65] *T. S. Lundy* and *J. I. Federer*, Trans. AIME *224*, 1285 (1962).

[66] *R. N. Ghostagore*, Phys. Rev. *155*, 603 (1967).

[67] *P. G. Shewmon* in: Fundamental Phenomena in the Materials Sciences. Vol. 3. Surface Phenomena. Plenum Press, New York 1966, p. 111ff.

[68] *C. E. Birchenall* and *J. M. Williams* in [67], p. 133ff.

[69] *G. Neumann* and *G. M. Neumann:* Surface Self-Diffusion of Metals. Diffusion Information Center, Solothurn 1972.

[70] *G. H. Frischat*, Glastech. Ber. *44*, 93 (1971).

[71] *G. H. Frischat* in: Amorphous Materials. Wiley-Interscience, London 1972, p. 235ff.

[72] *G. H. Frischat*, J. Amer. Ceram. Soc. *51*, 528 (1968).

[73] *A. D. Smigelkas* and *E. O. Kirkendall*, Trans. AIME *171*, 130 (1947).

[74] *H. Wever*, Angew. Chem. 75, 309 (1963); Angew. Chem. internat. Edit. 2, 288 (1963).
[75] *R. H. Doremus*, J. Phys. Chem. 68, 2212 (1964).
[76] *G. H. Frischat*, J. Mater. Sci. 6, 1229 (1971).
[77] *G. H. Frischat* and *U. Eichhorn*, unpublished results.
[78] *F. M. Ernsberger*, Glass Ind. 47, 422, 481, 542 (1966).
[79] *H. Schröder* and *G. Gliemeroth*, Naturwissenschaften 57, 533 (1970).
[80] *L. S. Darken*, Trans. AIME 185, 435 (1959).
[81] *A. K. Varshneya* and *A. R. Cooper*, J. Amer. Ceram. Soc. 55, 312 (1972).
[82] *J. Nölting*, Angew. Chem. 82, 498 (1970); Angew. Chem. internat. Edit. 9, 489 (1970).
[83] *J. Bardeen* and *C. Herring* in: Imperfections in Nearly Perfect Crystals. Wiley, New York 1952, p. 261ff.
[84] *L. W. Barr* and *A. D. LeClaire*, Proc. Brit. Ceram. Soc. 1, 109 (1964).
[85] *K. Compaan* and *Y. Haven*, Trans. Faraday Soc. 52, 786 (1956); 54, 1498 (1958).
[86] *R. J. Friauf*, Phys. Rev. 105, 843 (1957).
[87] *A. S. Miller* and *R. J. Maurer*, J. Phys. Chem. Solids 4, 196 (1958).
[88] *R. Steiger*, Chimia 18, 306 (1964).
[89] *M. D. Weber* and *R. J. Friauf*, J. Phys. Chem. Solids 30, 407 (1969).
[90] *J. P. Gracey* and *R. J. Friauf*, J. Phys. Chem. Solids 30, 421 (1969).
[91] *Y. Haven* and *B. Verkerk*, Phys. Chem. Glasses 6, 38 (1965).
[92] *N. L. Peterson, L. W. Barr*, and *A. D. LeClaire*, cited in [93].
[93] *L. W. Barr, J. N. Mundy*, and *A. H. Rowe* in: Amorphous Materials. Wiley-Interscience, London 1972, p. 243ff.
[94] *B. A. Thompson* and *R. L. Strong*, J. Phys. Chem. 67, 594 (1963).
[95] *C. Zener* in: Imperfections in Nearly Perfect Crystals. John Wiley, New York 1952, p. 289ff.
[96] *L. W. Barr, J. A. Morrison*, and *P. A. Schroeder*, J. Appl. Phys. 36, 624 (1965).
[97] *P. Süptitz*, Phys. Status Solidi 12, 555 (1965).
[98] *H. Bakker*, Phys. Status Solidi 28, 569 (1968).
[99] *S. J. Rothman, N. L. Peterson*, and *J. T. Robinson*, Phys. Status Solidi 39, 635 (1970).
[100] *G. Borchardt* and *H. Schmalzried*, Z. Phys. Chem. N. F. 74, 265 (1971).
[101] *B. Ilschner*, Festkörperprobleme 10, 415 (1970).
[102] *R. J. Charles*, J. Appl. Phys. 32, 1115 (1961).
[103] *B. Lengyel* and *Z. Boksay*, Z. Phys. Chem. 241, 36 (1969).

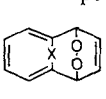
COMMUNICATIONS

Photooxidation of Annulenes

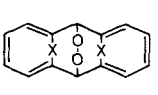
By *Emanuel Vogel, Arnold Alscher*, and *Klaus Wilms*[*]

Dedicated to Professor Hellmut Bredereck on the occasion of his 70th birthday

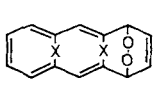
The bridged [4*n*+2]annulenes having a naphthalene[1] or an anthracene perimeter[2] resemble the classical aromatic compounds naphthalene and anthracene *inter alia* in being stable to atmospheric oxygen[3,4] and in exhibiting favorable steric conditions for 1,4-cycloadditions. It therefore seemed reasonable to assume that these annulenes, like certain naphthalenes and anthracene, undergo dye-sensitized photooxidation, *i.e.* reaction with singlet oxygen, to give 1,4-endoperoxides (1,4-epidioxy compounds) [*(1)* and *(2)* and/or *(3)*] or their reaction products[5]. As we have now found, the photooxidation behavior of bridged [10]- and [14]annulenes accords with expectations.



(1)

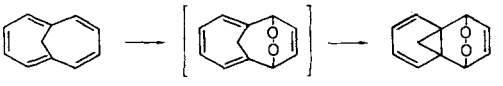


(2)



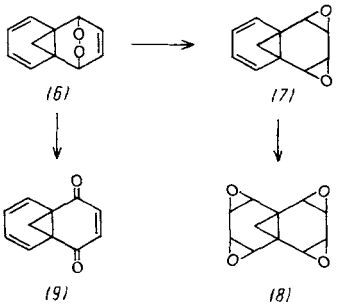
(3)

1,6-Methano[10]annulene *(4)*[6], which is remarkably stable to oxygen and is photostable in an inert gas atmosphere, undergoes fairly rapid oxidation on irradiation with a sodium vapor lamp in the presence of methylene blue and oxygen (methylene chloride; 10—15 °C)[7]. If the irradiated mixture is worked up below 15 °C the sole reaction product isolated is a sterically homogeneous 1,4-endoperoxide (*ca.* 25% after 12 h) whose NMR and UV spectra show it to possess the norcaradiene structure *(6)* [concerning the properties of *(6)* and the other photooxidation products mentioned in the text, see Table 1]. The peroxide group in *(6)* is apparently *anti* to the three-membered ring, for the cyclopropane protons of the compound accord well in their chemical shifts with those of the hydrocarbon tricyclo[4.3.1.0^{1,6}]deca-2,4-diene[8]. The 1,4-endoperoxide *(6)* is presumably formed by a [4+2] or [8+2] cycloaddition of singlet oxygen to *(4)* followed by a cycloheptatriene-norcaradiene valence isomerization of the resulting adduct *(5)*; however, the intermediacy of tricyclo[4.4.1.0^{1,6}]undeca-2,4,7,9-tetraene[9] instead of *(5)* cannot be completely ruled out.



(4) *(5)* *(6)*

In parallel to the behavior of related 1,4-endoperoxides[10] compound *(6)* yields the diepoxide *(7)* on gentle heating; *(7)* can be regarded as a trishomobenzene or trishomonaphthalene derivative. Under the photooxidation conditions employed with *(4)*, compound *(7)* is able to take up a further mole of singlet oxygen, albeit slowly, to give the tetraepoxide *(8)* *via* a 1,4-endoperoxide which has hitherto defied attempts at isolation. Since *(8)* exhibits only one AA'BB' system and a singlet in its NMR spectrum the two new epoxide rings are doubtless also *anti* to the cyclopropane ring. On attempted chromatography over alumina, compound *(6)* undergoes



(6) *(7)* *(9)* *(8)*

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Table 1. Properties of the photooxidation products.

Cpd.	M.p. [°C]	UV λ_{max} [nm] (ε)	60 MHz ^{1}H-NMR (τ) [ppm] (TMS internal standard)
(6)	colorless needles 139—140	270 (2535) (acetonitrile)	3.62 (m), 3.88 (s), 5.13 (m) 8.45 (d), 10.31 (d) ($CDCl_3$)
(7)	colorless needles 139—140	272 (2415) (acetonitrile)	3.88 (m), 6.45 (m), 6.57 (m) 8.37 (d), 10.04 (d) ($CDCl_3$; standard CH_2Cl_2)
(8)	colorless crystals 238—240 (dec.)		6.68 (m), 8.89 (s) (CD_2Cl_2)
(9)	yellow leaflets 110—111	225 (15630), 268 (2490), 326 (242), 363 (181), 405 (182) (dioxane)	3.16 (m), 3.48 (s), 3.84 (m), 7.35 (d), 9.22 (d) ($CDCl_3$)
(10)	colorless crystals 149—150	260 (4890) (acetonitrile)	3.5 (s), 6.38 (m), 6.6 (m) ($CDCl_3$)
(11)	colorless needles 175—176	255 (4655) (acetonitrile)	3.26—3.90 (m), 6.28—6.78 (m), 10.74 (s) ($CDCl_3$)
(14)	red needles 171—172	267 (46000), 325 (25400), 410 (3480) (dioxane)	2.61—2.88 (m), 2.64 (s), 3.45 (s), 5.29 (m), 8.80 (m), 9.96 (m) (CCl_4)
(16)	deep red needles 210—212	271 (29000), 328 (36800), 440 (2340) (dioxane)	2.7—3.4 (m), 3.90 (d), 5.20 (m), 8.58 (m), 9.52 (m) (CCl_4)
(17)	brown crystals 175—177	243 (6800), 306 (54200), 382 (7750) (dioxane)	0.33 (m), 0.55 (s), 2.6—3.5 (m), 5.76 (m), 8.62 (m), 9.24 (m) ($CDCl_3$)

dehydrogenation to give the known compound tricyclo[4.4.1.0^{1,6}]undeca-3,7,9-triene-2,5-dione *(9)*[11].

1,6-Oxido[10]annulene and 1,6-imino[10]annulene can be photooxidized only very slowly, probably because the $-I$ effect of the bridge oxygen and the bridge nitrogen, respectively, lower the tendency of these annulenes to undergo cycloadditions with singlet oxygen.

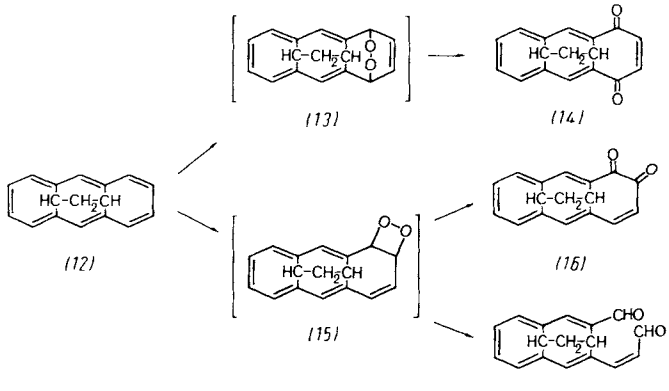


(10) *(11)*

The 1,4-endoperoxides derived from 1,6-oxido- and 1,6-imino[10]annulene show an even more pronounced tendency to rearrange thermally to diepoxides than *(6)*. Accordingly, attempts to isolate the peroxides have so far invariably afforded the isomers *(10)*[12] and *(11)*[13], respectively. To our knowledge, *(11)* is the first benzeneimine derivative in which the hydrogen on the nitrogen is not replaced by substituents.

The aromatic bridged [14]annulenes having an anthracene perimeter are also amenable to photooxidation, although with these compounds the reaction proceeds less uniformly than in the case of *(4)*. As a representative example we shall consider the behavior of 1,6:8,13-propanediylidene[14]annulene *(12)*. Irradiation of *(12)* in the presence of methylene blue and oxygen (methylene chloride; 10—15 °C) leads to complete reaction of the starting material within only 2—3 h giving a mixture of products which can be separated into the two [14]annulene quinones *(14)* (9%) and *(16)* (8%)[14] and the dialdehyde *(17)* (9%) by chromatography over silica gel.

The structures of the three photooxidation products *(14)*, *(16)*, and *(17)* follow from the NMR spectra in conjunction with the UV spectra and the detection of CO groups. In accord with the C_s symmetry of the molecule, the NMR spectrum of *(14)* (see Table 1) is relatively simple: as expected it shows only an AA'BB' system and two singlets for the perimeter protons. The coupling constants of the protons belonging to the AA'BB' system indicate that *(14)* contains the cycloheptatriene and not the norcaradiene partial structure. In the case of the less transparent spectra of *(16)* and *(17)*, crucial evidence for the structural elucidation was provided by the fact that the spectrum of *(16)* features an AB system among the signals of the perimeter protons, whereas that of *(17)* contains the signals of two (non-equivalent) aldehyde protons.



(13) *(14)* *(12)* *(16)* *(15)* *(17)*

The annulene quinone *(14)* is apparently a subsequent product of the initially formed 1,4-endoperoxide *(13)*. That a peroxide of type *(2)*, which would be the analog of 9,10-dihydro-9,10-epidioxyanthracene[15], or the respective quinone does not occur in detectable amounts among the reaction products is probably due to steric effects. The isomeric annulene quinone *(16)* and the dialdehyde *(17)* must arise from the 1,2-dioxetane *(15)*; however, it remains to be established whether *(15)* is a primary photooxidation product or whether it is formed from *(13)* in the process of isolation[16][**].

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[**] *Note added in proof* (June 14, 1974): As was subsequently found, *(14)*, *(16)*, and *(17)* are formed from *(13)* on the silica gel column.

[1] *E. Vogel*: Special Publ. No. 21, The Chemical Society, London 1967, p. 113.

[2] *E. Vogel*, Pure Appl. Chem. 28, 355 (1971).

[3] *anti*-1,6:8,13-Bismethano[14]annulene, which is non-aromatic due to steric inhibition of resonance, is an exception: *E. Vogel, M. Biskup, A. Vogel, U. Haberland*, and *J. Eimer*, Angew. Chem. *78*, 642 (1966); Angew. Chem. internat. Edit. *5*, 603 (1966).

[4] Most unbridged annulenes are sensitive to atmospheric oxygen, which probably accounts for the absence of any reports of photooxidations to give 1,4-endoperoxides in the case of these compounds.

[5] Concerning the formation of 1,4-endoperoxides with singlet oxygen see the following reviews: *K. Gollnick* and *G. O. Schenck* in *J. Hamer*: 1,4-Cycloaddition Reactions. Academic Press, New York 1967, p. 286; *J. Rigaudy*, Pure Appl. Chem. *16*, 169 (1968); *C. S. Foote, ibid. 27*, 635 (1971); *D. R. Kearns*, Chem. Rev. *71*, 395 (1971).

[6] For a detailed synthetic procedure see *E. Vogel, W. Klug*, and *A. Breuer*, Org. Synth., in press.

[7] Under similar irradiation conditions, 1,4-endoperoxide formation also occurs with hexamethyl- and octamethylnaphthalene: *H. Hart* and *A. Oku*, Chem. Commun. *1972*, 254.

[8] *E. Vogel, W. Wiedemann, H. D. Roth, J. Eimer*, and *H. Günther*, Liebigs Ann. Chem. *759*, 1 (1972).

[9] Concerning the question whether a 1,6-methyno[10]annulene-tricyclo[4.4.1.$0^{1,6}$]undeca-2,4,7,9-tetraene equilibrium exists, see: *H. Günther, H. Schmickler, F. A. Straube*, and *E. Vogel*, Angew. Chem. *85*, 585 (1973); Angew. Chem. internat. Edit. *12*, 570 (1973).

[10] *K. H. Schulte-Elte, B. Willhalm*, and *G. Ohloff*, Angew. Chem. *81*, 1045 (1969); Angew. Chem. internat. Edit. *8*, 985 (1969); *E. Vogel, H.-J. Altenbach*, and *C. D. Sommerfeld*, Angew. Chem. *84*, 986 (1972); Angew. Chem. internat. Edit. *11*, 936 (1972); *C. H. Foster* and *G. A. Berchtold*, J. Amer. Chem. Soc. *94*, 7939 (1972).

[11] *E. Vogel, W. A. Böll, E. Lohmar, B. Söhngen, K. Müllen*, and *H. Günther*, Angew. Chem. *83*, 401 (1971); Angew. Chem. internat. Edit. *10*, 398 (1971).

[12] Unpublished experiments in collaboration with Dipl.-Chem. *C. D. Sommerfeld*.

[13] Unpublished experiments in collaboration with Dipl.-Chem. *M. Ridder*.

[14] The redox behavior of *(14)* and *(16)* justifies our regarding these carbonyl compounds as quinones; *E. Vogel et al.*, to be published.

[15] *C. Dufraisse* and *H. Gérard*, Bull. Soc. Chim. Fr. *4*, 2052 (1937).

[16] *J. E. Baldwin, H. H. Basson*, and *H. Krauss, Jr.*, Chem. Commun. *1968*, 984; *J. Rigaudy* and *J. J. Basselier*, XXIIIrd International Congress of Pure and Applied Chemistry, Special Lectures, Vol. I, p. 383 (1971).

Effect of the Herbicide *N*-Phosphonomethylglycine on the Biosynthesis of Aromatic Amino Acids

By *Uta Roisch* and *Franz Lingens*[*]

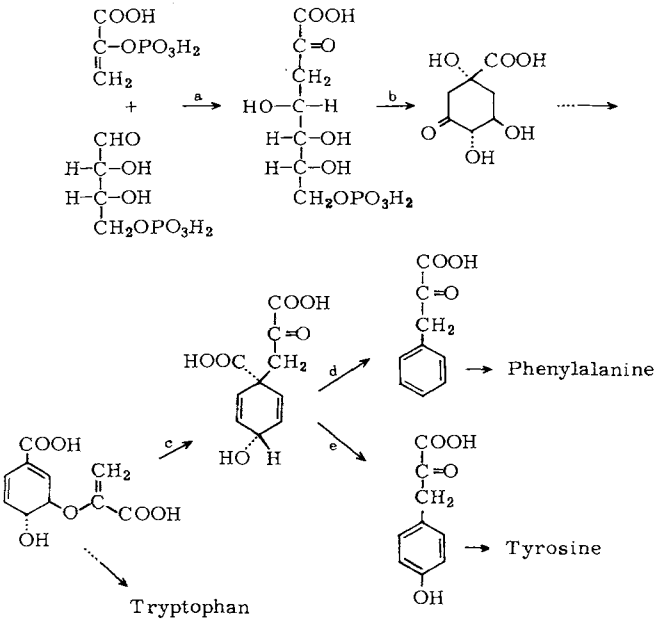
Dedicated to Professor Hellmut Bredereck on the occasion of his 70th birthday

The herbicide[1] *N*-phosphonomethylglycine *(1)* has proved particularly promising for destruction of perennial resistant weeds such as couch grass and bindweed.

$H_2O_3PCH_2-NH-CH_2-COOH$ *(1)*

From growth experiments with *Lemna gibba* and *Rhizobium japonicum*, *Jaworski*[2] concluded that the effect of this compound is due to inhibition of the biosynthesis of aromatic amino acids. The inhibitory action of *(1)* could be reversed by addition of aromatic amino acids.

We have studied which metabolic step is influenced by the herbicide (see Scheme 1). *N*-Phosphonomethylglycine *(1)* was synthesized as described by *Crofts* and *Kosolapoff*[3] and by *Edward*[4]. Growth of *Escherichia coli* B is completely inhibited for 16 h by *(1)* at a concentration of 2×10^{-3} M. This inhibitory effect is partially removed by addition of phenylalanine; tyrosine at the same concentration counteracts the inhibition to a lesser extent; the two amino acids have an increased effect if administered in admixture. The effect of



Scheme 1. Biosynthesis of phenylalanine, tyrosine, and tryptophan. Enzymes: a, 3-deoxy-2-oxo-D-arabinoheptonic acid 7-phosphate synthetase (E.C. 4.1.2.15); b, 5-dehydroquinic acid synthetase; c, chorismate mutase (E.C. 5.4.99.5); d, prephenate dehydratase (E.C. 4.2.1.51); e, prephenate dehydrogenase (E.C. 1.3.1.12).

tryptophan was slight, but nevertheless significant. The action of *(1)* can be eliminated completely by addition of a mixture of all three amino acids. No effect was observed with other amino acids (histidine, valine, leucine).

We have found that *(1)* inhibits the enzyme 3-deoxy-2-oxo-D-arabinoheptonic acid 7-phosphate synthetase (E.C. 4.1.2.15, test according to[5]); with 10^{-2} M *(1)* inhibition amounts to 50%. 5-Dehydroquinic acid synthetase (test according to[6]) is also inhibited by *(1)*. Both inhibitory effects are removed by addition of Co^{2+}.

Chorismate mutase (E.C. 5.4.99.5, test according to[7]), prephenate dehydrogenase (E.C. 1.3.1.12, test according to[8]), and prephenate dehydratase (E.C. 4.2.1.51, test according to[7]) are not affected by *(1)*.

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[1] *D. D. Baird, R. P. Upchurch, W. B. Homesley*, and *J. E. Franz*, Proc. Northcent. Weed Contr. Conf. *26*, 64 (1971).

[2] *E. G. Jaworski*, J. Agr. Food Chem. *20*, 1195 (1972).

[3] *P. C. Crofts* and *G. M. Kosolapoff*, J. Amer. Chem. Soc. *75*, 5738 (1953).

[4] *F. J. Edward*, DOS 2152826 (1972), Monsanto Co.

[5] *D. B. Sprinson, P. R. Srinivasan*, and *M. Katagiri*, Methods Enzymol. *5*, 394 (1962).

[6] *D. B. Sprinson, P. R. Srinivasan*, and *J. Rothschild*, Methods Enzymol. 5, 398 (1962).

[7] *R. G. H. Cotton* and *F. Gibson*, Methods Enzymol. *17 A*, 564 (1970).

[8] *J. Dayan* and *D. B. Sprinson*, Methods Enzymol. *17 A*, 562 (1970).

Addition of Oxoalkane Polyanions to Nitroolefins. A New Synthesis of Cyclohexanones [**]

By *Dieter Seebach* and *Volker Ehrig*[*]

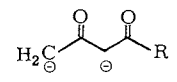
During our studies on the Michael addition of highly reactive organolithium compounds[1] to nitroolefins for the prepara-

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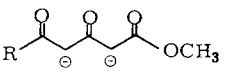
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[**] This work was supported by the Fonds der Chemischen Industrie.

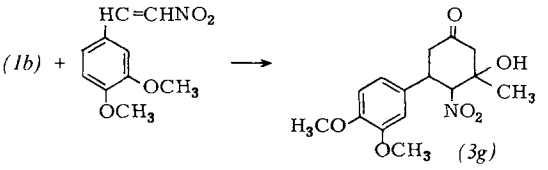
tion of alkaloid precursors, we examined the behavior of the polyanions *(1)* and *(2)*[2]. These species were obtained from 1,3-dicarbonyl derivatives by stepwise metalation.



(1a), R = H
(1b), R = CH_3



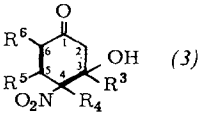
(2a), R = CH_3
(2b), R = $H_2C^{\ominus}$



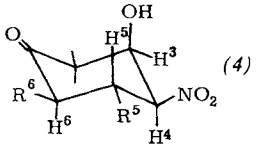
(3g)

Consecutive Michael addition and, after appropriate work-up (see *Experimental*), aldol reaction leads directly to the highly substituted cyclohexanones *(3)*; the synthesis of *(3g)* will serve as an example [for *(3a)—(3i)* see Table 1]. (The newly formed C—C bonds are emphasized by bold print in the formula.) The products *(3)* can readily be obtained pure owing to the pronounced ease with which they crystallize[3]. The spectroscopic data [*e.g.* IR: OH (br.) 3600—3200, C=O 1710, NO_2 1560 cm^{-1}] and elemental analyses are in accord with the proposed structures.

Surprisingly, neither the melting behavior nor the NMR spectra of the crude and pure products *(3)* gave any indication of the formation of diastereoisomers (up to four chiral centers). The configuration of the uniform products can in some cases be deduced from the NMR spectra (in D_6-DMSO or $CDCl_3$, for example see *Experimental*) [cf. formula *(4)*].



(3)



(4)

The typical[4] *gauche* ($J_{3\text{-H},4\text{-H}} = 2.5$ Hz) and *anti* coupling constants ($J_{4\text{-H},5\text{-H}}$, $J_{5\text{-H},6\text{-H}} = 12$ Hz) establish the *cis* relationship of OH and NO_2 in *(3b)* and *(3f)*, the *trans* relationship of NO_2 and R^5 in *(3a)—(3c)* and *(3e)—(3i)*, and the *trans* relationship of R^5 and R^6 in *(3h)*. No decision on the configuration about the C^3—C^4 bond of the ring in *(3a)*, *(3c)—(3e)*, *(3g)—(3i)* can be reached on the basis of the NMR spectrum.

5-(3,4-Dimethoxyphenyl)-3-hydroxy-3-methyl-4-nitrocyclohexanone (3g):

β-Nitro-3,4-dimethoxystyrene (1.16 g, 5.5 mmol) in THF (30 ml) is added to a stirred solution of *(1b)* (12 mmol) [prepared by consecutive metalation of 2,4-pentanedione (1.53 g) with NaH (0 °C) and *n*-butyllithium (−78 °C)] in THF (40 ml)/hexane (7 ml) under argon at −78 °C over 15 min. After 3 h the cold solution (−78 °C) is poured into water (250 ml), neutralized with acetic acid, and extracted with methylene chloride; yield 1.10 g (73%) of *(3g)*, m.p. 156—159 °C (from CH_2Cl_2/ether). IR (KI): 3350 (OH, broad), 1715 (C=O), 1560 and 1365 cm^{-1} (NO_2). NMR ($CDCl_3$): δ = 6.80 (2 aromatic H, s), 6.72 (1 aromatic H, s), 5.00 (H^4, d, 12 Hz), 3.96 (H^5, m), 3.80 ($2OCH_3$, 2 s, 0.015 ppm separation); 3.0 (OH, br. s); 2.4—2.8 ($2H^2$, $2H^6$, m), 1.40 (3H (CH_3), s).

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[1] *D. Seebach* and *H. F. Leitz*, Angew. Chem. *81*, 1047 (1969); *83*, 542 (1971); Angew. Chem. internat. Edit. *8*, 983 (1969); *10*, 501 (1971).

[2] Cf. *T. M. Harris et al.*, J. Org. Chem. *31*, 1032 (1966); J. Amer. Chem. Soc. *89*, 6734 (1967); *95*, 6865 (1973), and further literature cited therein.

[3] The open-chain adducts can be isolated if glacial acetic acid is added at low temperature, the mixture allowed to warm to 0 °C and then worked up in aqueous solution; only open-chain products can be prepared by addition of secondary acetamide and acetoacetic ester dianions (*D. Seebach* and *V. Ehrig*, to be published).

[4] *W. F. Trager et al.*, J. Org. Chem. *30*, 3257 (1965).

Table 1. Starting compounds, yields (not optimized), and melting points of the cyclohexanones *(3)*.

Nitroolefin	Poly-anion	*(3)*	R^3	R^4	R^5	R^6	Yield [%]	M.p. [°C]
Nitroethylene	*(1b)*	*a*	CH_3	H	H	H	18	117.0–120.5
Nitropropene	*(1a)*	*b*	H	H	CH_3	H	42	117.4–118.0
1-Nitropropene	*(1b)*	*c*	CH_3	H	CH_3	H	60	116.0–116.5
2-Nitropropene	*(1b)*	*d*	CH_3	CH_3	H	H	35	113–115
β-Nitrostyrene	*(1b)*	*e*	CH_3	H	C_6H_5	H	55	157.5–161.0
β-Nitro-3,4-methylenedioxystyrene	*(1a)*	*f*	H	H	3,4-methylenedioxyphenyl	H	58	186–190 (dec.)
β-Nitro-3,4-dimethoxystyrene	*(1b)*	*g*	CH_3	H	3,4-dimethoxyphenyl	H	73	156–159
β-Nitro-3,4-dimethoxystyrene	*(2a)*	*h*	CH_3	H	3,4-dimethoxyphenyl	$COOCH_3$	40	179–181 (dec.)
β-Nitro-3,4-dimethoxystyrene	*(2a)*	*i*	CH_2COOCH_3	H	3,4-dimethoxyphenyl	H	40	134–136

Sulfonylbis(imidosulfur Oxide Difluoride) from Trichlorophosphazosulfonylimidosulfur Oxide Difluoride[**]

By *Christof Jäckh* and *Wolfgang Sundermeyer*[*]

We have already utilized the reaction of mercury bis(imidosulfur oxide difluoride) *(1)*[1] with element halides to prepare numerous imidosulfur oxide difluorides[2,3] not previously accessible by other methods. Compound *(1)* also reacts quantitatively with trichlorophosphazosulfonyl chloride *(2)*[4] to give trichlorophosphazosulfonylimidosulfur oxide difluoride *(3)*.

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$$Hg(NSOF_2)_2 + 2Cl{-}SO_2{-}NPCl_3 \rightarrow 2F_2OSN{-}SO_2{-}NPCl_3 + HgCl_2 \quad (1)$$
(1) (2) (3)

Compounds *(1)* (0.1 mol) and *(2)* (0.2 mol) are heated to 70 °C for 9 h in dry carbon tetrachloride (200 ml). After cooling, the mercury chloride is removed (G 3 frit) in the absence of air and the solvent drawn off under vacuum. Pure *(3)* remains as a yellowish viscous liquid which is sensitive to hydrolysis and decomposes above 100 °C during distillation at 0.01 torr. The compound was identified by elemental analysis and its mass spectrum: m/e = 320/318/316/314 molecular ion (rel. int. 0.09/2.7/7.3/6.4 %), 283/281/279 $F_2OSN{-}SO_2{-}NPCl_2$ (0.08/5.5/6.4), 220/218/216/214 $SO_2{-}NPCl_3$ (5.5/34.6/98/100), 164 $F_2OSN{-}SO_2$ (5.5), 150 $NPCl_3$ (5.5), 115 $NPCl_2$ (3.6), 100 $NSOF_2$ (3.7), 80 NPCl (9.1), 67 OSF (10.9), 66 PCl (3.6), 64 SO_2 (9.0), 62 NSO (5.5), 48 SO (7.3), 46 SN (14.5), and 45 NP (5.3). The ^{19}F-NMR spectrum displays a singlet at −45.8 ppm in $CFCl_3$ (external standard), and the IR spectrum bands at 1415, 1365, 1240, 1190, 880, 850, 775, 630, 600, 555, 540, and 510 cm^{-1}.

Neither the reaction of sulfonyl chloride with *(1)* nor that of sulfamide or doubly symmetrically substituted sulfamide, nor that of $F_2OSN{-}SO_2{-}NCO$[3], with sulfur oxide tetrafluoride *(4)*[5] has yet afforded sulfonylbis(imidosulfur oxide difluoride) *(5)*. We have now obtained *(5)* by cleavage of the trichlorophosphazo group in *(3)* by OSF_4.

$$F_2OSN{-}SO_2{-}NPCl_3 + OSF_4 \rightarrow F_2OSN{-}SO_2{-}NSOF_2 + [F_2PCl_3] \quad (2)$$
(3) (4) (5) (6)

The reaction presumably involves formation of *(6)* which, however, reacts further with *(4)*. This course is evidenced by analysis of the by-products.

$$2[F_2PCl_3] + 3OSF_4 \rightarrow 2PF_5 + 3OSF_2 + 3Cl_2 \quad (3)$$
(6) (4)

Accordingly, a corresponding excess of *(4)* should enhance the yield of *(5)*. This is found not to apply in practice.

Heating of a mixture of *(3)* (0.1 mol) and *(4)* (0.1 mol) to 80 °C for 10 h in a 100-ml autoclave, the volatile products being drawn off into a cold trap after the reaction mixture has cooled, followed by distillation of the volatile components together with the liquid residue found in the autoclave affords a low yield (*ca.* 2 g, 7.5 %) of *(5)*, b.p. 49 °C/12 torr. The substance was identified by elemental analysis and its mass spectrum: m/e = 266/264 molecular ion (rel. int. 2.7/14.5 %), 166/164 $F_2OSN{-}SO_2$ (10.9/100), 100 $NSOF_2$ (9.1), 86 OSF_2 (1.8), 83 SO_2F (1.6), 67 SOF (12.8), 64 SO_2 (1.8), 48 SO (2.7), and 46 SN (2.7). The transition 264→164 is confirmed by a metastable peak at 101.9.—The ^{19}F-NMR spectrum contains a singlet at −46.2 ppm in $CFCl_3$ (ext. standard), and the bands of the IR spectrum appear at 1435, 1265, 1090, 880, 815, 730, 708, 695, 550, and 532 cm^{-1}.

An indication that the reaction proceeds according to eq. (2), and for the formation of fluorophosphoranes such as *(6)*, was also provided by the reaction of triphenylphosphazo derivatives such as $(CH_3)_3Si{-}NP(C_6H_5)_3$[6] or $Cl{-}SO_2{-}NP(C_6H_5)_3$ with OSF_4, where triphenyldifluorophosphorane is formed instead of triphenyloxophosphorane. Application of this reaction to trichlorophosphazo derivatives thus opens up an additional method for the preparation of imidosulfur oxide difluorides. For example, compound *(2)* reacts with *(4)* according to

$$Cl{-}SO_2{-}NPCl_3 + OSF_4 \rightarrow F{-}SO_2{-}NSOF_2 + [FPCl_4] \quad (4)$$
(2) (4) (7)

giving fluorosulfonylimidosulfur oxide difluoride *(7)*[7].

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[1] *K. Seppelt* and *W. Sundermeyer*, Angew. Chem. *82*, 931 (1970); Angew. Chem. internat. Edit. *9*, 905 (1970).

[2] *W. Sundermeyer, A. Roland*, and *K. Seppelt*, Angew. Chem. *83*, 443 (1971); Angew. Chem. internat. Edit. *10*, 419 (1971).

[3] *A. Roland* and *W. Sundermeyer*, Z. Naturforsch. *27b*, 1102 (1972).

[4] *A. V. Kirsanov*, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk *1950*, 426; Chem. Abstr. *45*, 1503d (1951).

[5] *A. Roland*, Dissertation, Universität Heidelberg 1972.

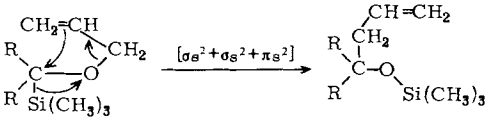
[6] *W. Lidy*, unpublished experiments.

[7] *O. Glemser, H. W. Roesky*, and *P. R. Heinze*, Angew. Chem. *79*, 723 (1967); Angew. Chem. internat. Edit. *6*, 710 (1967).

Rearrangement of (Trimethylsilyl)methyl Allyl Ethers, A Dyotropic Reaction?

By *Manfred T. Reetz* [*]

Recently dyotropic rearrangements were defined as pericyclic processes in which two σ-bonds interchange their positions[1]. In order to test whether such reactions are feasible, allyl ethers of type *(1)* containing silyl and allyl moieties as potential migrating groups were synthesized[2]. These groups were chosen to ensure that rearrangement should be thermally allowed according to orbital symmetry[3,4].



(1) *(2)*

(a), R + R = *o*, *o'*-biphenylylene
(b), R = phenyl

Heating of *(1)* in inert solvents up to 160—200 °C did indeed afford the silyl ethers *(2)*[5] (yields: *(2a)*, 98 %; *(2b)*, 97 %). Despite the absence of appreciable amounts of side products, the rearrangement does not proceed according to a single mechanism, since the rearrangement of *(1a)* (α,α-D_2) afforded *(2a)* with only 80 % allyl inversion. The origin of the "wrong" isomer was explained by cross-over experiments which revealed that migration of the silyl groups is 100 % intramolecular, while that of the allyl groups is only 72 % intramolecular. In contrast, thermolysis in the presence of a radical trapping agent (benzoquinone) furnished *(2a)* in *ca.* 60 % yield, but *completely intramolecularly with more than 97 % allyl inversion*[6].

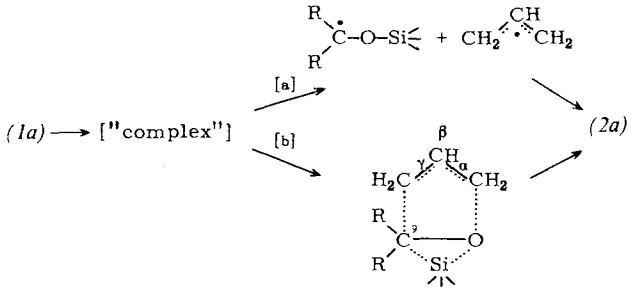
The rearrangement of *(1a)* in the absence of a radical trapping agent obeys first order kinetics, and is influenced only slightly by solvent polarity: k_{rel} = 1.0 (decalin): 1.2 (benzene): 2.8 (*o*-dichlorobenzene): 5.1 (propylene carbonate). Thus ions or zwitterions can be ruled out as possible intermediates. The activation parameters (measured in benzene) have the values

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$E_a = 32.3 \pm 0.6$ kcal mol^{-1}, $\Delta H^{\neq} = 31.4 \pm 0.6$ kcal mol^{-1}, $\Delta S^{\neq} = -8.9 \pm 0.8$ cal deg^{-1}.

The secondary kinetic deuterium isotope effect of $k_H/k_D = 1.05 \pm 0.03$ measured for *(1a)* (α,α-D_2) (160 °C, benzene) shows that the allyl C—O bond can be stretched only to a slight extent in the transition state. The corresponding effect of $k_H/k_D = 1.00 \pm 0.03$ measured for *(1a)* (γ,γ-D_2) also excludes appreciable bond formation between the allyl C^{γ} atom and the fluorenyl C^9 atom in the transition state.



Although the present results do not permit final conclusions regarding the mechanism, it appears certain that in the rearrangement the initial motion of the silyl group is far more advanced than that of the allyl group. Rate-determining formation of a short-lived complex, in which the silyl moiety coordinates with the O-atom, followed by rapid decomposition into radicals[7] (path [a]) or intramolecular concerted rearrangement (path [b]) is conceivable.

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[1] *M. T. Reetz*, Angew. Chem. *84*, 161, 163 (1972); Angew. Chem. internat. Edit. *11*, 129, 131 (1972).

[2] Prepared from the corresponding (bromo)methylsilanes by reaction with allyl alcohol in the presence of silver sulfate.

[3] *R. B. Woodward* and *R. Hoffmann*, Angew. Chem. *81*, 797 (1969); Angew. Chem. internat. Edit. *8*, 781 (1969).

[4] This treatment considers only the orbitals of the σ- and π-framework, and neglects the d orbitals of silicon and n orbitals of oxygen. Concerning the role of d and n orbitals in dyotropic rearrangements, see: *M. T. Reetz*, Tetrahedron *29*, 2189 (1973).

[5] The structure of *(2)* was established spectroscopically, analytically, and by independent syntheses.

[6] Molar ratio benzoquinone: *(1a)* = 0.4 : 1 (in benzene). Even with a ten-fold increase in benzoquinone concentration the yield of *(2a)* remained at 60%.

[7] Path [a] represents a homolysis with neighboring group participation. This rare reaction type is currently being investigated with the benzyl ethers corresponding to *(1)*.

Subhalides of Tellurium: Crystal Structures of α-TeI and β-TeI

By *Rüdiger Kniep*, *Dietrich Mootz*, and *Albrecht Rabenau*[*]

After elucidating the crystal structures of Te_3Cl_2 and Te_2X (X = Cl, Br, or I)[1] we have now completed determination of the structures of the remaining known subhalides of tellurium[1].

Phase studies in the system Te—TeI_4[2] have shown that TeI is the only thermodynamically stable phase of the pseudobinary system. The phase width previously assumed for "Te_xI" could not be confirmed; instead it was proved that this is a further phase of 1:1 stoichiometry which was formed together with Te_2I in the same preparation. The compound that is stable with respect to the phase diagram (TeI in[1]) is now called α-TeI; the compounds β-TeI (Te_xI in[1]) and Te_2I[1] are metastable[2].

The crystals used for structure analysis of β-TeI and α-TeI were prepared hydrothermally in concentrated hydriodic acid[4]; their lattice constants have been given previously[1]. Although according to IR and Raman investigations of α-TeI[5] the crystal structure was not likely to possess an inversion center, the result of our complete structure analysis justifies its description in the centrosymmetric space group $P\bar{1}$. The structure of β-TeI is also centrosymmetric, having space group C2/m.

For determination of the crystal structure of β-TeI the intensities of 779 independent reflections with $Mo_{K\alpha}$ radiation ($\theta_{max} = 30°$) were measured on an automatic single-crystal diffractometer. After corrections for absorption and anisotropic refinement the *R* factor amounts to 5.4%.

Figure 1 represents the macromolecular structural unit of this structure. It consists of a zigzag chain of Te atoms running parallel to the crystallographic *b* axis, the atoms having alternate square-planar and trigonal-pyramidal coordination. Correspondingly, there are two independent I atoms in bridging and terminal positions respectively. Formally the β-TeI building unit is generated by halving the Te_2I unit[6] along its length and occupying the free valences each by one I atom.

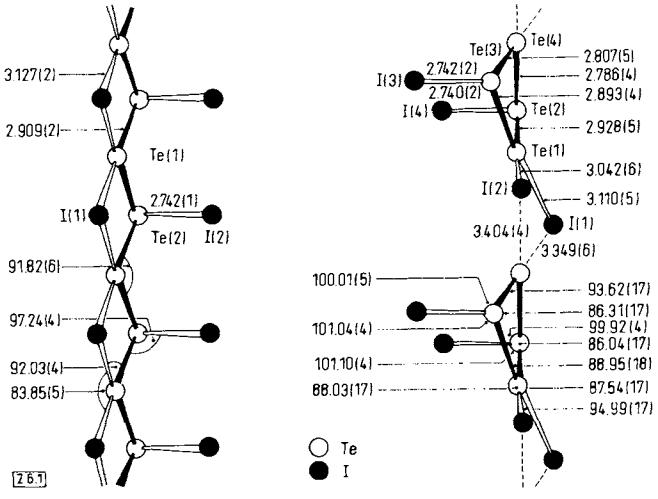


Fig. 1. Structural unit of β-TeI (left) and α-TeI (right): bond lengths (Å) and bond angles (°) with standard deviations in parentheses.

For determination of the crystal structure of α-TeI 3233 reflections were measured with $Mo_{K\alpha}$ radiation ($\theta_{max} = 30°$). After anisotropic refinement the *R* factor amounts to 5.5%.

Figure 1 shows a section of the molecular association in the α-TeI structure parallel to the crystallographic *c*-axis. It is interesting that here the structural unit is not macromolecular but a small molecule Te_4I_4. A Te_4 ring is formed, whose Te atoms are coordinated in three different ways: Te(1) square-planar, Te(2) and Te(3) trigonal-pyramidal, Te(4) only two-fold. The distances between I(1) and I(2) and the bivalent tellurium of the neighboring molecule in the *z*-direction are the shortest intermolecular contacts; they link the molecules into chains along the crystallographic *c*-axis.

That the four-membered ring in α-TeI consists only of Te atoms becomes clear from a comparison of the bond lengths and angles with those of β-TeI and from considerations of

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the mechanism of the transformation β→α observed in single crystals[7]. This atomic assignment is also indicated by a qualitative interpretation of the electrical conductivities of all the tellurium subhalides[8, 9]. The concept of modified tellurium structures[1] is useful in such considerations: graded similarities to and differences from the structure of elemental tellurium are reflected in the conductivities.

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[1] *R. Kniep, D. Mootz,* and *A. Rabenau,* Angew. Chem. *85*, 504 (1973); Angew. Chem. internat. Edit. *12*, 499 (1973).

[2] *R. Kniep, A. Rabenau,* and *H. Rau,* J. Less-Common Metals *35*, 325 (1974).

[3] *A. Rabenau, H. Rau,* and *P. Eckerlin,* Angew. Chem. *79*, 688 (1967); Angew. Chem. internat. Edit. *6*, 706 (1967).

[4] *R. Kniep, D. Mootz,* and *A. Rabenau,* XXIVth IUPAC Congr., Hamburg, September 2—8, 1973.

[5] *W. Bauhofer* and *R. Kniep,* Mater. Res. Bull. *8*, 989 (1973).

[6] Te_2I [1] here became the key substance because the differentiation of Te from I followed from the structure determination of the isotypic Te_2Br and also because the results thus achieved could be applied to the interpretation of the β- and α-TeI structures.

[7] The structural course of this topotactic reaction has not yet been completely formulated and experimentally checked. It seems certain, though, that the cohering fragment I(1)-I(1)'-Te(1)-Te(2)-Te(2)'-I(2)-I(2)' ($I \doteq x, 1+y, z$) of the β-TeI building unit already constitutes the α-TeI molecule up to (but not including) the Te(4) atom required for the Te_4 ring closure.

[8] *U. v. Alpen* and *R. Kniep,* Sol. State Comm., in press.

[9] *U. v. Alpen, R. Kniep,* and *E. Gmelin,* DPG Conference, Freudenstadt, April 1—5, 1974.

3*H*-3-Benzazonine and the 3-Benzazoninyl Anion[**]

By *A. G. Anastassiou* and *E. Reichmanis*[*]

In the area of nonbenzenoid aromatics direct comparison of a given member with benzene in terms of π-electron delocalization is normally judged to constitute a reliable, albeit demanding, test of "aromatic" character. Recently, we demonstrated[1] that of all known heteronins *(1)*, X = heteroatom, only 1*H*-azonine *(1a)*[2] and the corresponding base, the azoninyl anion *(1b)*[3], may be classified as "aromatic", with the latter slightly more so than the former. Presently, we offer direct comparison between these two species and benzene with a description of the title substances.

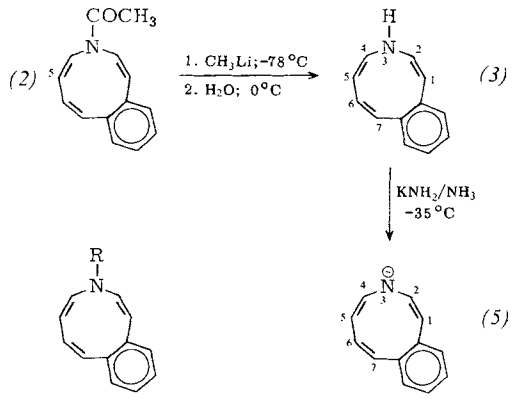


(1a), X = NH
(1b), X = $\overset{\ominus}{N}$

3*H*-3-Benzazonine *(3)* was prepared by treatment of the corresponding acetamide *(2)*[4] with methyllithium in THF at −78 °C followed by aqueous quenching at 0 °C. It was isolated as an air-sensitive pale yellow viscous oil displaying the following spectral characteristics: λ_{max} (hexane) = 290 nm ($\varepsilon \approx 2000$); ^{1}H-NMR (60 MHz; D_6-acetone/D_2O): $\tau = 2.71$ (4H, s), 3.55 (d, 1H^7, $J_{7,6} = 11.5$ Hz), 3.90 (d, 1H^6, $J_{6,7} \approx 11.5$ Hz)[5], 3.92 (d, 1H^2, $J_{2,1} = 10.5$ Hz), 4.37 (d, 1H^4, $J_{4,5} = 10.0$ Hz), 4.72 (d, 1H^1, $J_{1,2} = 10.5$ Hz), and 5.71 (d, 1H^5, $J_{5,4} = 10.0$ Hz)[5]; *m/e* 169 (M^+; 43%). Chemically, the structure of *(3)* was confirmed through conversion to the methoxycarbonyl derivative *(4a)*[4] (NMR, IR) on successive treatment with methyllithium and methyl chloroformate.

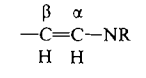
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[**] We thank the National Science Foundation and the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.



(4a), R = $COOCH_3$
(4b), R = $CON(CH_3)_2$

The region of NMR resonances associated with the azonine moiety of *(3)* serves to establish the molecule as an unexceptional benzopolyene. It is noted, for example, that the NMR signals due to the α ($\tau = 3.92$ and 4.37) and β protons ($\tau = 4.72$ and 5.71) of *(3)* are significantly displaced to higher field relative to their counterparts in the spectrum of 1*H*-azonine *(1a)* ($\tau = 2.93$ for H^α and 4.00 for H^β)[1, 3]. Moreover, unlike 1*H*-azonine whose NMR spectrum is displaced to lower fields relative to those of its *N*-substituted variants[1], comparison of *(3)* with its *N*-substituted derivatives, *(2)*, *(4a)*, and *(4b)*, in terms of H^5, *i.e.*, the β proton least likely to be influenced by the benzene group, actually reveals an upfield shift in the case of the parent and one which satisfies the linear correlation between $\delta(H_\beta)$ and σ_p^- (*N*-substituent, R = H, $CON(CH_3)_2$, $COOCH_3$, $COCH_3$) recently shown[6] to be characteristic of the isolated



function[7]. The nine-membered segment of *(3)* emerges as polyenic also on the basis of the UV spectrum (290 nm) which shows the type of mild bathochromic shift, by comparison with those of its derivatives *(2)* (275 nm), *(4a)* (267 nm), and *(4b)* (288 nm), one might expect chiefly on the basis of decreased heteroatom electronegativity in the absence of major skeletal changes.

Attention in this project was next directed towards the preparation of the corresponding base of *(3)*, namely the anion *(5)*, in the hope that the attendant reduction in heteroatom electronegativity might provide the necessary driving force for the development of a delocalized heteronin skeleton in spite of the adverse effect of benzannelation.

Exposure of *(3)* to potassium amide in liquid ammonia at *ca.* −35 °C changes the NMR spectrum from that described earlier for *(3)* (see above)[8, 9] to one consisting of absorptions at[10]: $\tau = 2.4$—2.7 (m), 2.8—3.1 (m), 3.38 (d, H^2, $J_{2,1} = 10$ Hz), 3.6—4.1 (m, $H^6 + H^7$), 3.72 (d, H^4, $J_{4,5} = 8.5$ Hz), 5.10 (d, H^1, $J_{1,2} = 10$ Hz), and 6.23 (dd, H^5, $J_{5,4} = 8.5$ Hz, $J_{5,6} = 4.5$ Hz) in relative areas of *ca.* 2:2:1:2:1:1:1. Convincing chemical proof that the species displaying the new spectrum is the benzazoninyl anion *(5)* was obtained by the regeneration of the original spectrum, *i.e.*, that of *(3)*, on rapid addition of a cold (*ca.* −70 °C) ammonia solution of *(5)* to moist ether at 0 °C.

It is immediately obvious from the NMR spectrum of *(5)* that the nine-membered segment of the molecule does not sustain a ring current at the temperatures employed in this

study (< -30 °C)[11]. This is best evidenced by the *upfield* shift of β protons H^1 (by 23 Hz) and H^5 (by 32 Hz) on going from *(3)* to *(5)*, which simply reflects the increased availability of the lone pair for limited delocalization but is clearly inconsistent with the development of the diamagnetic ring current expected of this system.

Obviously, the present findings indicate that neither 3-benzazonine *(3)*, at ambient temperature, nor the corresponding base *(5)*, generated at *ca.* −70 °C and observed at −35 °C[11], are capable of sustaining a ring current, *i.e.*, they are no more than benzopolyenes under the experimental conditions employed here.

(6)   *(7)*

Interestingly the behavior of *(3)* and *(5)* sharply contrasts with that of their iso-π-electronic carbocycle, the benzocyclononatetraenyl anion *(6)* which was recently shown[12] to possess a well delocalized 14π frame exhibiting strong ring diamagnetism over a wide temperature range (−55 to +35 °C).

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[1] *A. G. Anastassiou*, Accounts Chem. Res. *5*, 281 (1972).

[2] *A. G. Anastassiou* and *J. H. Gebrian*, Tetrahedron Lett. *1970*, 825.

[3] *A. G. Anastassiou* and *S. W. Eachus*, J. Amer. Chem. Soc. *94*, 2537 (1972).

[4] *A. G. Anastassiou*, *E. Reichmanis*, and *R. L. Elliott*, Tetrahedron Lett. *1973*, 3805.

[5] The signal shows secondary splitting.

[6] *A. G. Anastassiou* and *R. L. Elliott*, J. C. S. Chem. Commun. *1973*, 601.

[7] In CCl_4 the H^5 resonance shows at $\tau = 5.71$ in *(3)*, 5.22 in *(4b)*, 5.18 in *(4a)*, and 5.10 in *(2)*.

[8] The NMR spectrum of *(3)* in liquid ammonia is very similar to that recorded in D_6-acetone. Most importantly, the chemical shifts of key β protons H^1 and H^5 are the same in the two media.

[9] In the generation of *(5)*, as described here, it is essential that the conversion of potassium to KNH_2 be complete, since potassium metal was found to activate efficient denitrogenation of *(5)* or *(3)* to benzocyclooctatetraenyl dianion *(7)* (NMR). For comparison purposes this dianion was prepared independently on exposure of benzocyclooctatetraene to potassium in liquid ammonia (−40 °C) and was found to possess a well delocalized 14π frame by NMR [$\tau = 2.05$ (2H, dd, $J = 7$ Hz, 3.5 Hz), 3.25 (d, H^5, H^{10}, $J_{5,6} = 11.5$ Hz), and 3.5—4.3 (6H, m)]. Exposure of the dianion prepared by either method to water at 0 °C affords three distinct benzocyclooctatrienes.

[10] The chemical shifts in liquid ammonia were determined by employing dimethoxyethane as internal standard.

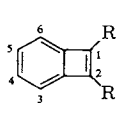
[11] If *(5)* is allowed to stand overnight at 0 °C, its NMR spectrum undergoes radical changes. The structural characterization of the compound(s) responsible for the development of the new spectrum is currently under way.

[12] *A. G. Anastassiou* and *R. C. Griffith*, J. Amer. Chem. Soc. *96*, 611 (1974).

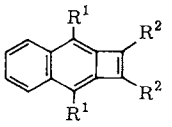
Isolation of 3,4,5,6-Tetramethyl-1,2-diphenylbenzocyclobutadiene

By *Henner Straub*[*]

Apart from metal complexes, no stable derivatives of benzocyclobutadiene *(1a)* are known[1]; only the naphtho[*b*]cyclobutadienes *(2a)* and *(2b)* have been isolated so far. Resonance energy calculations[2] on *(1a)* and *(1b)* indicate such a pronounced stabilizing effect of the two phenyl groups that isolation of compound *(1b)* does not appear to be a futile undertaking[3].

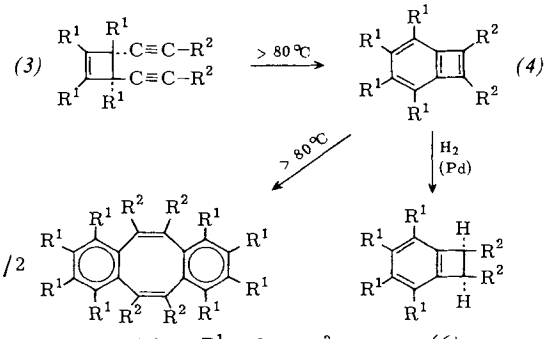


(1a), R = H
(1b), R = C_6H_5



(2a), R^1 = H; R^2 = C_6H_5
(2b), R^1 = C_6H_5; R^2 = Br

We were recently able to show by means of trapping reactions that thermal dimerization of the *trans*-bisacetylene *(3)* in boiling cyclohexane proceeds *via* the permethylated 1,2-diphenylbenzocyclobutadiene *(4)*[4]. Meanwhile we have found that the valence isomerization *(3)* → *(4)* is complete within a few minutes at *ca.* 110 °C, whereas the dimerization of *(4)* to *(5)* still progresses relatively slowly at this temperature. Timely quenching of the reaction mixture to room temperature permits isolation of the benzocyclobutadiene *(4)* in 20% yield[5] in the form of carmine red needles (m. p. 120 °C, dec.). *(4)* undergoes significant decomposition in solution at room temperature, even in the absence of air[6], but is surprisingly stable in crystalline form and transforms to the dimer *(5)*—without melting—only above 80 °C.



(5) R^1 = CH_3, R^2 = C_6H_5 *(6)*

The hydrocarbon *(4)*[7] has remarkable spectroscopic properties: the mass spectrum shows the molecular ion *m/e* 310 and the associated isotopic peak, but no significant fragmentation. The ^{1}H-NMR spectrum (CH_2Cl_2) displays a multiplet at $\delta = 7.15$—7.45 (10H) for the aromatic protons and only *one* singlet at $\delta = 1.93$ (12H) for the four methyl groups. This signal, which appears at relatively high field, has previously been observed for the starting material *(3)*[4] in high temperature measurements. In the IR spectrum (KBr) the $\nu_{C=C}$ stretching modes of the aromatic nuclei are accompanied by two further bands at 1660 and 1475 cm^{-1} which do not appear in the spectrum of the hydrogenation product *(6)*. In the UV region [*n*-hexane, nm (log ε)][6] *(4)* absorbs at 201 (4.66), 218 sh (4.38), 278 (4.60), and less strongly at 468 (3.25). The red compound *(2a)*[8] also absorbs *inter alia* at similarly long wavelengths [436 (371), 455 (3.71) in ethanol]. These long-wave bands are apparently characteristic of condensed 1,2-diphenylcyclobutadiene systems.

Chemical proof of the structure of *(4)* is based, apart from trapping reactions[4], on catalytic hydrogenation with palladium on calcium carbonate in which *(4)* rapidly takes up one mole of hydrogen to form the colorless benzocyclobutene *(6)* (m. p. 159 °C)[7]. The structure of *(6)* is confirmed by mass, IR, UV, and in particular by its ^{1}H-NMR spectrum [2.02 (s, 6H), 2.22 (s, 6H), 4.95 (s, 2H), 6.83 (s, 10H) in CCl_4]. As for the nonmethylated *cis*-1,2-diphenylbenzocyclobutene[9], the *cis* configuration of *(6)* is deduced from the characteristic upfield shift of the phenyl signals.

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The extent to which the four methyl groups in *(4)* contribute to stabilization of the skeleton *(1b)* is difficult to estimate. However, the effect cannot be very large since the intermediate 3,4,5,6-tetramethylbenzocyclobutadiene undergoes immediate angular dimerization[10] like *(1a)*.

3,4,5,6-Tetramethyl-1,2-diphenylbenzocyclobutadiene (4)

All operations and measurements have to be performed under nitrogen. A solution of *(3)* (3.1 g, 10 mmol)[4] in light petroleum (b.p. 110—130 °C, 150 ml) is first heated to 110 °C (oil bath 175—180 °C) for 9 min and then immediately cooled in an ice bath. After complete removal of solvent (3—1 torr at room temperature) the residue is rapidly dissolved in light petroleum (b.p. 60—80 °C) and freed from sparingly soluble *(5)* (*ca.* 30%) by filtration. The filtrate is concentrated (14 torr at room temperature) until the onset of crystallization. The mixture is then cooled to −20 °C and the carmine red needles filtered off under suction (m.p. 120 °C, dec.); yield 20%.

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[1] *M. P. Cava* and *M. J. Mitchell*: Cyclobutadiene and Related Compounds. Academic Press, New York 1967; *D. Seebach* in *Houben-Weyl-Müller*: Methoden der Organischen Chemie. Thieme, Stuttgart 1971, Vol. IV/4, p. 231.

[2] See, *e.g.*: *M. J. S. Dewar* and *G. J. Gleicher*, Tetrahedron *21*, 1817 (1965); *A. Y. Meyer*, *ibid.* *24*, 6215 (1968), and further references therein.

[3] Unsuccessful attempted synthesis of *(1b)*: *M. Stiles*, *U. Burckhardt*, and *A. Haag*, J. Org. Chem. *27*, 4715 (1962).

[4] *A. Huth*, *H. Straub*, and *E. Müller*, Liebigs Ann. Chem. *1973*, 1893; *A. Huth*, Dissertation, Universität Tübingen 1972.

[5] If *(4)* is trapped in solution directly with reactive dienophiles, the yields of the adducts exceed 80% in some cases [4].

[6] The UV spectra were each recorded 3 min after dissolution of *(4)*. The extinction coefficients of the bands change when the solution is allowed to stand, ε_{201} and ε_{218} increasing and ε_{278} and ε_{468} decreasing. The decrease in ε_{468} of a *ca.* 0.4 mM solution affords a half-life of *ca.* 23 min for *(4)* at room temperature.

[7] Correct elemental analyses were obtained for *(4)* and *(6)*.

[8] This does not apply to *(2b)*; *M. P. Cava* and *H. Y. Hwang* in ref. [1], p. 246.

[9] *G. Quinckert*, *K. Opitz*, *W.-W. Wiersdorff*, and *M. Finke*, Liebigs Ann. Chem. *693*, 44 (1966).

[10] *H. Straub*, unpublished results.

Chiral Macrobicyclic and Macrotricyclic Ligands[**]

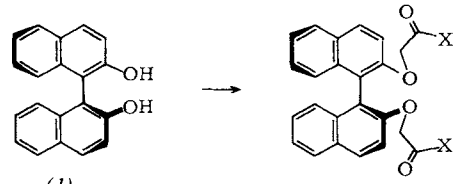
By *Bernard Dietrich*, *Jean-Marie Lehn*, and *Jacques Simon*[*]

Complexation of alkali and alkaline-earth cations[1] by macrocyclic[2], macrobicyclic[1,3], and macrotricyclic[4–6] ligands leads to the formation of inclusion complexes of the cryptate[3] type. The design of molecular receptors capable of *molecular recognition* represents the next step in the elaboration of synthetic ligands which may selectively complex a given substrate molecule[5,6]. An interesting special case is the design of optically active substances capable of functioning as *chirospecific molecular receptors; i.e.* substances which display preferential complexation of one optical antipode of a given substrate. Optically active macrocyclic amino-ether[7] and polyether[8,9] ligands have been described recently; the latter display pronounced selectivity of complexation of chiral substrates[9]. Such behavior is also known for the natural macrocyclic polysugars, the cyclodextrins[10].

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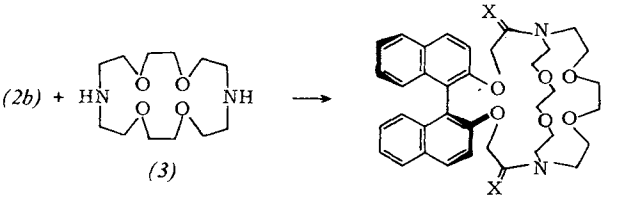
[**] Molecular Receptors, Part 3. Reported in part at the First Fall Organic Chemistry Meeting of the American Chemical Society, October 1—3, 1973, North Falmouth, Massachusetts.—Part 2: ref. [6].

We present here our results on the synthesis and on some properties of the chiral macrobicyclic and macrotricyclic molecules *(4)* and *(6)*, which may function as ligands for metal cations[1,3,6] as well as for molecules[6]. The binaphthyl group has been selected as center of chirality in the recently described chiral macrocyclic polyethers[8,9]. Not only does it introduce marked chirality into a molecule but is also quite easily prepared and resolved[11], and confers increased lipophilicity upon the system. Other chiral groups may be used for similar purposes[12].



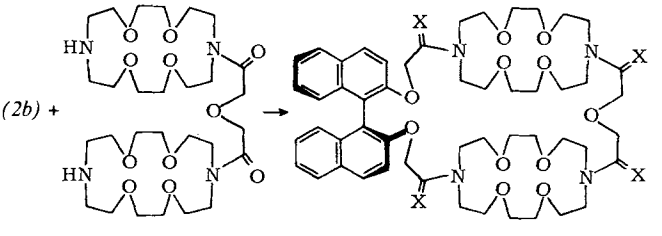
(1) *(2a)*, X = OH *(2b)*, X = Cl

Optically active (*S*)-(−)-1,1′-bi-2-naphthol *(1)* [m.p. 206 °C; $[\alpha]_{578}^{25}$ −40° (*c* = 0.5, THF); −39.6° (*c* = 1.05, THF)[11]] has been obtained *via* resolution of its phosphoric acid derivative with cinchonine[11] and recrystallized from toluene. Condensation of *(1)* with bromoacetic acid in refluxing methanol in the presence of potassium carbonate affords the optically active dicarboxylic acid *(2a)* [m.p. (racemic) ≈210 °C; $[\alpha]_D^{25}$ −36° (*c* = 0.22, acetone); yield 95%]. The corresponding dichloride *(2b)* is obtained by treatment with oxalyl chloride in benzene; the yield is quantitative (NMR spectrum) and the oily product is used without further purification; the crystalline racemic dichloride has m.p. 73—75 °C.



(3) *(4a)*, X = O *(4b)*, X = H_2

Condensation of *(2b)* with the macrocyclic diamine *(3)*[3] under high dilution conditions[3] gives the macrobicyclic dicarboxamide *(4a)* [m.p. 190—192 °C; $[\alpha]_D^{25}$ −92° (*c* = 0.41, $CHCl_3$); yield 60%]. Reduction of *(4a)* with diborane in THF[3] leads to the optically active macrobicyclic diamine *(4b)* [oil; $[\alpha]_D^{25}$ −151° (*c* = 0.39, $CHCl_3$); yield 90%].



(5) *(6a)*, X = O *(6b)*, X = H_2

High dilution condensation[3] of *(2b)* with the diamine *(5)*[5] affords the tetracarboxamide *(6a)* [glass; $[\alpha]_D^{25}$ −42° (*c* = 0.23, acetone); yield 50%]. Diborane reduction[3] of *(6a)* gives

the optically active macrotricyclic tetraamine *(6b)* [oil; $[\alpha]_D^{25}$ $-68°$ ($c=0.17$, $CHCl_3$); yield 90%]. Compounds *(4b)* and *(6b)* were further purified by lyophilization in benzene/methanol (9:1). The spectral (NMR; mass) and analytical data of the compounds described are in agreement with the structures *(2)*, *(4)*, and *(6)*. Control experiments were performed to ensure that no detectable racemization occurs in the course of the condensation and reduction steps leading to *(2a)*, *(4b)*, and *(6b)*.

Hydrolysis of the borane-amine adducts formed in the diborane reductions was not effected under reflux (as in ref.[3]); instead the products were treated with a mixture of THF and 9 N HCl (1:1) for one hour at 25°C. The amines *(4b)* and *(6b)* were extracted with toluene after the solution had been rendered basic.

Compounds *(4)* and *(6)* are the first optically active, synthetic macrobicyclic and macrotricyclic substances to be reported. Macrotricyclic systems contain a large intramolecular cavity which should be capable of accommodating substrate molecules[5,6]. Molecular models show that the cavity of compounds *(6)* forms a deep (about 8 Å) chiral pocket. Like their previously described achiral analogs[1,3,5], *(4b)* and *(6b)* complex various metal cations.

Formation of complexes between ligand *(4b)* and the bromides of sodium, potassium, rubidium, and cesium leads to marked changes in the NMR and UV spectra of the ligand. An interesting effect is found for the optical rotation. The element of chirality is the angle between the two naphthalene systems in the binaphthyl fragment. Complexation of a metal cation inside the molecular cavity is expected to affect the optical activity of *(4b)* both by electronic effects and by modification of the chirality angle. The latter factor may be expected to display a gradual variation as the size of the included cation increases from sodium to cesium and deforms the ligand, the charge remaining constant. This is indeed observed: $[\alpha]_D^{25}=+36$, -9, -130, and $-215°$ (in $CHCl_3$) for the cryptate complexes of *(4b)* with NaBr, KBr, RbBr, and CsBr, respectively. Assuming that the value measured for Na^+ contains both the effect of cation charge and that of conformational change on cation inclusion, the variations observed for K^+, Rb^+ and Cs^+ may be related to a progressive opening of the dihedral angle caused by the increase in cation size. Complexation also leads to large changes in the circular dichroism spectra of the ligand.

The macrotricyclic ligand *(6b)* also shows pronounced NMR spectral changes on cation complexation (Na^+, K^+). The specific rotation is -25 and $0°$ for the Na^+ and K^+ complexes respectively. Like the previously described tetraamides[5,6], *(6a)* does not form stable complexes with alkali metal cations. However, it contains amide (like peptides) and ether binding sites and has been found to extract ammonium salts from water solution into chloroform[13]. Both cation and anion properties are expected to affect such ion pair binding. So far only low optical resolution (about 10% optical purity) of racemic substrates has been achieved[13].

Depending on the properties desired, additional structural features may be introduced into these ligands (*e.g.* cationic or anionic sites for substrate-ligand ion pairing and catalytic sites for specific reactions), as has been done for macrocyclic polyethers (carboxylate sites)[8,9] and for macropolycyclic amino-ethers (carboxylate, imidazole, and hydroxamate sites)[14].

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[1] *J. M. Lehn*, Struct. Bonding *16*, 1 (1973).

[2] *C. J. Pedersen* and *H. K. Frensdorff*, Angew. Chem. *84*, 16 (1972); Angew. Chem. internat. Edit. *11*, 16 (1972).

[3] *B. Dietrich, J. M. Lehn, J. P. Sauvage*, and *J. Blanzat*, Tetrahedron *29*, 1629 (1973); *B. Dietrich, J. M. Lehn*, and *J. P. Sauvage, ibid. 29*, 1647 (1973), and references therein.

[4] *J. Cheney, J. M. Lehn, J. P. Sauvage*, and *M. E. Stubbs*, J. C. S. Chem. Commun. *1972*, 1100.

[5] *J. M. Lehn, J. Simon*, and *J. Wagner*, Angew. Chem. *85*, 621 (1973); Angew. Chem. internat. Edit. *12*, 578 (1973).

[6] *J. M. Lehn, J. Simon*, and *J. Wagner*, Angew. Chem. *85*, 622 (1973); Angew. Chem. internat. Edit. *12*, 579 (1973).

[7] *F. Wudl* and *F. Gaeta*, J. C. S. Chem. Comm. *1972*, 107.

[8] *E. P. Kyba, M. G. Siegel, L. R. Sousa, G. D. Y. Sogah*, and *D. J. Cram*, J. Amer. Chem. Soc. *95*, 2691 (1973); *R. C. Helgeson, J. M. Timko*, and *D. J. Cram, ibid. 95*, 3023 (1973); *G. M. Gokel* and *D. J. Cram*, J. C. S. Chem. Comm. *1973*, 481.

[9] *E. P. Kyba, K. Koga, L. R. Sousa, M. G. Siegel*, and *D. J. Cram*, J. Amer. Chem. Soc. *95*, 2692 (1973); *R. C. Helgeson, K. Koga, J. M. Timko*, and *D. J. Cram*, J. Amer. Chem. Soc. *95*, 3021 (1973).

[10] *F. Cramer*, Angew. Chem. *68*, 115 (1956); *F. Cramer* and *G. Mackensen*, Angew. Chem. *78*, 641 (1966); Angew. Chem. internat. Edit. *5*, 601 (1966); Naturwissenschaften *54*, 625 (1967), and references therein; *R. Breslow*, Chem. Soc. Rev. *1*, 553 (1972); *H. P. Benschop* and *G. R. Van den Berg*, Chem. Commun. *1970*, 1431; *M. Mikołajczyk, J. Drabowicz*, and *F. Cramer*, Chem. Commun. *1971*, 317.

[11] *J. Jacques, C. Fouquey*, and *R. Viterbo*, Tetrahedron Lett. *1971*, 4617.

[12] *V. Prelog*, personal communication.

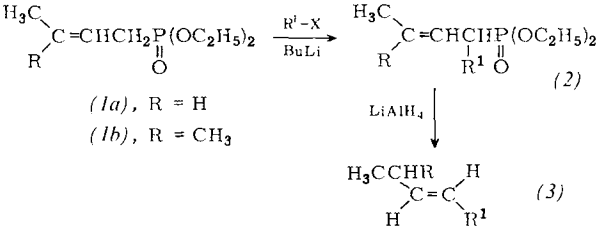
[13] *J. M. Lehn* and *J. Simon*, to be published.

[14] *J. M. Lehn, F. Montavon, P. Vitali*, and *J. Wagner*, unpublished results.

A Novel Method for the Stereoselective Synthesis of *trans* Olefins

By *Kiyosi Kondo, Akira Negishi*, and *Daiei Tunemoto*[*]

We report herein a new and useful two-step synthesis of *trans* olefins from alkyl halides R^1—X and γ-substituted allylphosphonates, *e. g.* diethyl 2-butenylphosphonate *(1a)* and diethyl (3-methyl-2-butenyl)phosphonate *(1b)*.



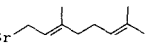
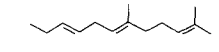
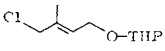
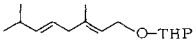
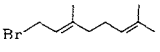
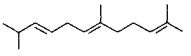
There are several reports in the literature describing electrophilic capture of phosphonate-stabilized carbanions by alkyl halides or ketones[1]. However, those adducts do not appear to be satisfactorily transformed into olefins[2]. We found that lithio derivatives of γ-substituted allylphosphonates such as *(1a)* or *(1b)* were alkylated at the α position exclusively by a variety of alkyl halides. Furthermore, the adducts *(2)* undergo a smooth reductive fission to olefins *(3)* on treatment with $LiAlH_4$ in dry ether at 0°C for a few hours. The IR spectra exhibited a strong absorption at 965 cm^{-1} characteristic of *trans* olefins; their homogeneity was confirmed by gas chromatography using several different columns.

Thus the newly found hydrogenolysis of allylic phosphonates, in conjunction with alkylation as described above, constitutes an excellent and generally applicable method for the stereoselective synthesis of *trans* olefins[3] (Table 1).

A further advantage of the method derives from the fact that even if the starting material *(1)* is not stereochemically

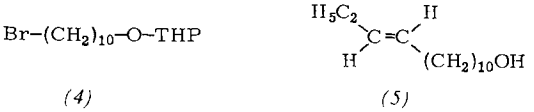
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Table 1. Yields of the reaction products from allylphosphonates *(1)* and alkyl halides X—R^1.

(1)	X—R^1	*(2)* Yield [%]	*trans*-Olefin *(3)*	Yield [%]
(1a)	$Br—CH_2C_6H_5$	83	$CH_3CH_2CH=CH—CH_2C_6H_5$	89
(1a)	$Br—(CH_2)_7CH_3$	92	$CH_3CH_2CH=CH—(CH_2)_7CH_3$	56
(1a)		78		82
(1a)	$Br—CH_2CH(OC_2H_5)_2$	35	$CH_3CH_2CH=CH—CH_2CH(OC_2H_5)_2$	40
(1b)	$Cl—CH_2C_6H_5$	55	$(CH_3)_2CHCH=CH—CH_2C_6H_5$	82
(1b)	 [a]	67		77
(1b)	$Br—(CH_2)_7CH_3$	94	$(CH_3)_2CHCH=CH—(CH_2)_7CH_3$	84
(1b)		91		83

[a] THP tetrahydropyran-2-yl.

pure reduction of *(2)* still affords pure *trans* olefin. For example, alkylation of a mixture of *cis*- and *trans*-2-butenylphosphonate *(1a)* with benzyl bromide followed by reduction afforded *trans*-1-phenyl-2-pentene exclusively[4].



(4) *(5)*

Finally, the present method was applied to the synthesis of *trans*-11-tetradecenal, which is the sex attractant of the eastern spruce budworm, *Choristoneura fumiferana Clemens*[5]. Starting with readily available bromide *(4)*[6] and *(1a)*, and using the same procedure as described above, we obtained *trans*-11-tetradecenol *(5)* in 73% yield, which was readily converted into the aldehyde in 95% yield.

trans-1-Phenyl-2-pentene (3), R = H, $R^1 = CH_2C_6H_5$

n-Butyllithium (12 mmol) was added to a stirred solution of *(1a)* (1.92 g, 10 mmol) in THF (20 ml) at −60 °C under a positive pressure of argon and stirred at this temperature for 1 h. Benzyl bromide (1.7 g, 10 mmol) in THF (5 ml) was added dropwise to the solution. After stirring for an additional 30 min at −60 °C, the reaction mixture was allowed to warm to room temperature. The mixture was quenched by the addition of 10% aqueous NH_4Cl and the product was isolated by extraction with ether. Distillation of the crude product afforded 2.33 g (83%) of the adduct *(2)*, R = H, $R^1 = CH_2C_6H_5$ (b. p. 144 °C/0.3 torr). A solution of this adduct (1.4 g, 5 mmol) in dry ether (100 ml) was cooled in an ice bath and $LiAlH_4$ (0.11 g) was added. After stirring for 1 h at 0 °C, a few drops of water were added and the resulting mixture was filtered through celite. The solid was washed with ether and the combined filtrates were evaporated. The resulting crude product was purified by distillation to yield 0.65 g (89%) of *(3)*, R = H, $R^1 = CH_2C_6H_5$ (b. p. 88 °C/14 torr). The overall yield of the olefin did not decrease when the two steps were performed successively without purification of the intermediate.

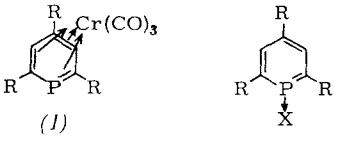
Received: March 15, 1974 [Z 20 IE]
German version: Angew. Chem. 86, 415 (1974)

[1] *G. Lavielle*, C. R. Acad. Sci. *C 270*, 86 (1970).
[2] *E. J. Corey* and *G. T. Kwiatkowski*, J. Amer. Chem. Soc. *88*, 5654 (1966).
[3] *J. Reucroft* and *P. G. Sammes*, Quart. Rev. Chem. Soc. *25*, 135 (1971), and references cited therein.
[4] *P. Vittorelli, T. Winkler, H. J. Hansen*, and *H. Schmid*, Helv. Chim. Acta *51*, 1457 (1968).
[5] *J. Weatherston, W. Roelofs, A. Comeau*, and *C. J. Sanders*, Can. Entomol. *103*, 1741 (1971).
[6] *F. L. M. Pattison, J. B. Stothers*, and *R. G. Woolford*, J. Amer. Chem. Soc. *78*, 2255 (1956).

Bis(1,2,4,6-tetraphenyl- and Bis(1-methyl-2,4,6-triphenyl-λ⁵-phosphorinyl)iron

By *Gottfried Märkl* and *Claus Martin*[*]

Phosphorins (phosphabenzenes) from transition metal complexes with coordination *via* both the π-electron system, as in the π-aromatic complex *(1)*[1], and the free electron pair, as in complexes of type *(2)*[2] and *(3)*[3]. In contrast, pyridine-transition metal π-complexes have hitherto only been accessible by indirect methods[4].

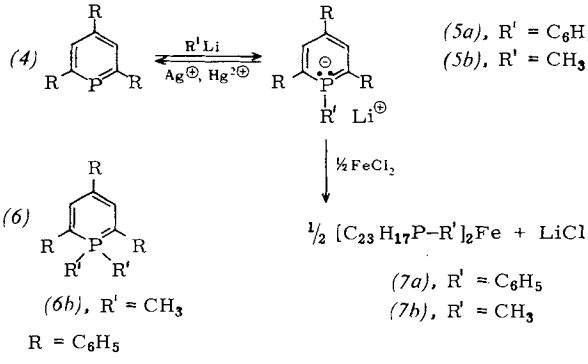


(1)

R = C_6H_5

(2a), X = $Cr(CO)_5$
(2b), X = $Mo(CO)_5$
(2c), X = $W(CO)_5$
(3a), X = AuCl
(3b), X = AuI

We have studied the reaction of 1,2,4,6-tetraphenyl-λ⁵-phosphorin-1-yllithium *(5a)* and the corresponding 1-methyl compound *(5b)* with the transition metal salts $AgNO_3$, $Hg(OAc)_2$, and $FeCl_2$.



(6)

(6b), R' = CH_3

R = C_6H_5

(5a), R' = C_6H_5
(5b), R' = CH_3

$\frac{1}{2}$ $[C_{23}H_{17}P–R']_2Fe$ + LiCl

(7a), R' = C_6H_5
(7b), R' = CH_3

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The anions[5] of *(5a)* and *(5b)*, which are sensitive to moisture, can be obtained as deep blue-red solutions by reaction of 2,4,6-triphenylphosphabenzene *(4)* with phenyl- and methyllithium, respectively, in benzene or THF; they can be isolated as relatively stable deep red salts of the tetrabutylammonium ion[6].

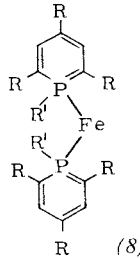
(5a) and *(5b)* undergo redox reactions with $AgNO_3$ and $Hg(OAc)_2$; silver or mercury is deposited and the phosphorin *(4)* regenerated. It has yet to be established whether σ-complexes having P—Ag or P—Hg bonds play an intermediate role in these reactions.

Treatment of *(5a)* and *(5b)* with $FeCl_2$ in THF (reaction conditions as for ferrocene formation from cyclopentadienyl anion and $FeCl_2$) affords deep brown solutions from which brownish red neutral compounds *(7a)* and *(7b)* can be isolated by chromatography (SiO_2/light petroleum); they form fine, felted, lustrous needles on crystallization from benzene/light petroleum.

(7a), m.p. 231 °C; mass spectrum (70 eV, T_0 = 180 °C): 858 (M^+, 5%); ^{1}H-NMR: τ = 2.34—3.57 (m, 40H), 4.72 (br. d, 4 phosphorin-H), $^3J_{P\ H}$ = 10 Hz.

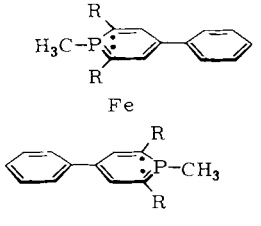
(7b), m.p. 192 °C; mass spectrum (70 eV, T_0 = 160 °C): 734 (M^+, 21%); ^{1}H-NMR: τ = 2.15—3.20 (m, 30H), 4.63 (br. d, 4 phosphorin-H), $^3J_{P-H}$ = 8 Hz, 9.96 (d, 6H), $^2J_{P-H}$ = 5 Hz (methyl-H).

The results of elemental analysis, osmometric molecular-weight determination, and mass spectrometry clearly indicate a metathetic reaction yielding $[C_{23}H_{17}P—R']_2Fe$. The ^{1}H-NMR spectrum of *(7b)* permits tentative conclusions regarding structure. Whereas the methyl protons of 1,1-dimethyl-2,4,6-triphenyl-λ^5-phosphorin *(6b)* appear as a doublet at τ = 8.27, the corresponding signal of *(7b)* exhibits a pronounced upfield shift (τ = 9.96).



(8)

R = C_6H_5



(7b)

We consider that this effect is interpretable only by assuming that the P—CH_3 groups are located directly above the phenyl substituents, as depicted, the methyl protons thus experiencing strong diamagnetic shielding. Similar conditions are found in 1,4-poly(methylenebenzenes)[7] and 1,6-methanocyclodecapentaenes[8]. The shift of the phosphorin proton signal from τ = 1.93 in *(4)* to 4.72 in *(7a)* and 4.63 in *(7b)* accords with observations on the π-complex *(1)* (τ = 4.0[11]).

The ^{31}P-NMR signals of *(7a)* lie at +45 ppm (relative to external H_3PO_4) and those of *(7b)* at +55 ppm. Since σ-complexation of phosphanes (PR_3) with carbonylmetal compounds leads to distinctly negative coordination shifts of the ^{31}P resonance [$(C_6H_5)_3P$, $\delta^{31}P$ = +6.0 ppm; $(C_6H_5)_3PCr(CO)_5$, −55.3 ppm; $[(C_6H_5)_3P]_2Ni(CO)_2$, −32.6 ppm[9]], the values for *(7a)* and *(7b)* contraindicate σ-bonded iron in the formally conceivable structure *(8)*.

The large ^{31}P upfield shift in *(7a)* and *(7b)* relative to the λ^5-phosphorins *(6)*, R' = alkyl or aryl [$\delta^{31}P$ = +6.0 ppm] is comparable with the considerable gain in shielding of the P atom on going from the phosphorin *(4)* (−178.2 ppm) to the π-complex *(1)* (−4.3 ppm). These data and the findings of ^{1}H-NMR spectroscopy strongly suggest structure *(7)* with central bonding of the iron over the phosphorin 6π system resembling that in dibenzenechromium and the metallocenes.

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[1] *J. Deberitz* and *H. Nöth*, Chem. Ber. *103*, 2541 (1970).

[2] *J. Deberitz* and *H. Nöth*, J. Organometal. Chem. *49*, 453 (1973).

[3] *K. C. Dash, J. Eberlein*, and *H. Schmidbaur*, Synth. Inorg. Metalorg. Chem. *1973*, 375.

[4] *E. O. Fischer* and *K. Öfele*, Chem. Ber. *93*, 1156 (1960).

[5] The anions of *(5)* and the 1,1-disubstituted phosphorins *(6)* having a formal $3d_\pi$—$2p_\pi$ double bond are isoelectronic. According to CNDO/2 calculations [*A. Schweig* and *H. Oehling*, Tetrahedron Lett. *1970*, 4941] the λ^5-phosphorins *(6)* are aromatic 6π systems with $s^{0.30}p^{0.48}d^{0.22}$ hybridization at the P atom.

[6] *C. Martin*, Dissertation, Universität Regensburg, planned for 1974.

[7] *J. S. Waugh* and *R. W. Fessenden*, J. Amer. Chem. Soc. *79*, 846 (1957).

[8] *E. Vogel* and *H. D. Roth*, Angew. Chem. *76*, 145 (1964); Angew. Chem. internat. Edit. *3*, 228 (1964); *W. Grimme, H. Hoffmann*, and *E. Vogel*, Angew. Chem. *77*, 348 (1965); Angew. Chem. internat. Edit. *4*, 354 (1965).

[9] *V. Mark, C. H. Dungan, M. M. Crutchfield*, and *J. R. van Wazer*, Top. Phosphorus Chem. *5*, 227 (1967), especially p. 414; see also [2].

Preparation and Reactions of Trifluoromethanesulfonic Arenesulfonic Anhydrides[1][**]

By *Franz Effenberger* and *Klaus Huthmacher*[*]

Dedicated to Professor Hellmut Bredereck on the occasion of his 70th birthday

In the course of our investigations on new electrophilic agents, we have reported on the preparation of trifluoromethanesulfonic carboxylic anhydrides and their high acylating potential[2]. We have now succeeded in obtaining the mixed sulfonic anhydrides *(3)* from sulfonyl bromides *(1)* and silver trifluoromethanesulfonate *(2)*.

$$\underset{(1)}{R\text{–}SO_2Br} + \underset{(2)}{AgOSO_2CF_3} \xrightarrow[-AgBr]{} R\text{–}SO_2\text{–}O\text{–}SO_2CF_3 \quad (3)$$

$$(3) \xrightarrow{+Ar\text{–}H,\ HOSO_2CF_3} R\text{–}SO_2\text{–}Ar \quad (4)$$

Since the anhydrides *(3)* are not stable in pure form, exact physical data cannot be given; their structure, however, is established unequivocally by ^{1}H-NMR and by their reaction with arenes, yielding aryl sulfones *(4)* (Table 1).

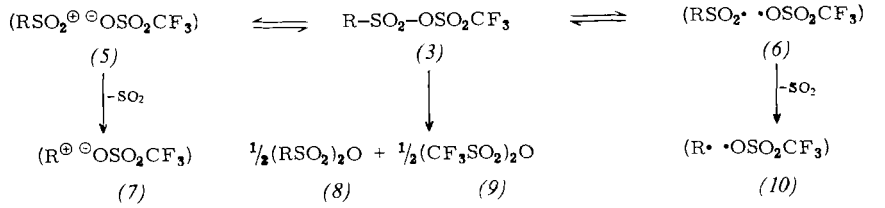
The extraordinary sulfonylating potential of the anhydrides *(3)* is apparent from the reaction with an arene as unreactive as chlorobenzene, which is sulfonylated in high yield even at 0 °C (see Table 1). With sulfonyl halides, on the other hand, sulfones are formed from arenes only at elevated temperature and in the presence of Friedel-Crafts catalysts[3].

The anhydrides *(3)* are thermolabile; in the absence of arenes which can be sulfonylated they decompose in various ways depending on the nature of R.

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For R = alkyl, heterolytic dissociation to *(5)* and subsequent loss of SO_2 yielding *(7)* are observed; the decomposition temperature falls as the stabilization of the carbenium ion



$R^{\oplus}$ increases. Radicals *(10)* are formed preferentially from anhydrides with polyalkyl- and polyalkoxyarenesulfonic components, probably by homolysis to *(6)* and loss of SO_2. The anhydrides listed in Table 1 suffer disproportionation into *(8)* and *(9)* upon warming. Since this process already occurs at temperatures slightly above 50 °C, the anhydrides *(3)* cannot be prepared from *(2)* and the less reactive sulfonyl chlorides.

Table 1. Preparation of trifluoromethanesulfonic arenesulfonic anhydrides *(3)* and their reaction with arenes to form sulfones *(4)* [a].

Starting materials		Products *(4)*		
(1), R =	Ar—H	sulfone	yield [%]	m. p. [°C] [b]
4-NO_2—C_6H_4—	benzene	4-nitrodiphenyl	34	142—143
4-Cl—C_6H_4—	benzene	4-chlorodiphenyl	80	94
C_6H_5—	benzene	diphenyl	90	126
4-CH_3—C_6H_4—	benzene	4-methyldiphenyl	98	126—127
4-CH_3—C_6H_4—	*p*-xylene	2,5,4′-trimethyldiphenyl	98	108
4-CH_3—C_6H_4—	toluene	di-*p*-tolyl [c]	100	
4-CH_3—C_6H_4—	chlorobenzene	4-chloro-4′-methyldiphenyl [d]	80	123—124

[a] The anhydrides *(3)* were prepared from *(1)* and *(2)* at 0 °C in nitromethane, and reacted with a threefold excess of arene (Ar—H) at the same temperature. The yields were determined by GLC. The yields obtained on a preparative scale are only slightly lower.
[b] The melting points of the sulfones *(4)* are in accordance with literature data. Mixed melting points with authentic material show no depression.
[c] Isomer distribution: 2,4′ : 3,4′ : 4,4′ = 42 : 5 : 53.
[d] No other isomers could be detected.

4-Methyldiphenyl sulfone, (4): R = p-tolyl, Ar = phenyl

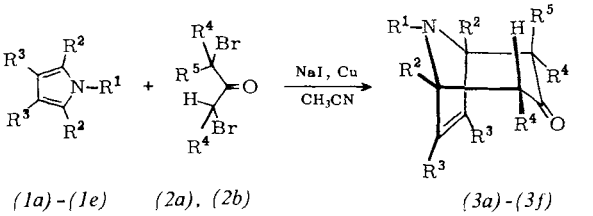
Compound *(2)* (2.56 g, 0.01 mol) is dissolved in nitromethane (10 ml) at 0 °C, and a solution of *p*-toluenesulfonyl bromide (2.35 g, 0.01 mol) in nitromethane (10 ml) is added. After 30 min stirring, benzene (2.34 g, 0.03 mol) is added. Stirring is continued for another 30 min, chloroform (20 ml) is added, the AgBr precipitate seperated, and the organic phase is washed with sodium carbonate solution and with water. The solvent is stripped off and the residue recrystallized from ethanol: yield 2.15 g (93 %), m. p. 126—127 °C (127—128 °C[4]); mixed m. p. 127 °C.

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A New Tropinone Synthesis[**]

By *Gérard Fierz*, *Ross Chidgey*, and *H. M. R. Hoffmann*[*]

We have developed a strikingly simple and versatile synthesis of tropinones which utilizes common starting materials and proceeds under neutral conditions at room temperature. Quite generally, the reductive dehalogenation of α,α′-dibromo ketones *(2a)* and *(2b)* with sodium iodide in the presence of pyrroles *(1a)*—*(1e)* and copper has been found to produce a variety of 6,7-dehydrotropinones *(3a)*—*(3f)*[1]. The adducts *(3)* are sensitive and tend to decompose on prolonged standing, especially when exposed to air, but they can be conveniently stored as hydrochlorides at 0 °C and also be purified in the same way (Table 1).



(1a)-(1e) *(2a), (2b)* *(3a)-(3f)*

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[1] Electrophilic Substitution of Aromatic Compounds, Part 9.—Part 8: *F. Effenberger*, *H. Klenk*, and *P. L. Reiter*, Angew. Chem. *85*, 819 (1973); Angew. Chem. internat. Edit. *12*, 775 (1973).

[2] *F. Effenberger* and *G. Epple*, Angew. Chem. *84*, 294 (1972); Angew. Chem. internat. Edit. *11*, 300 (1972).

[3] *F. R. Jensen* and *G. Goldman* in *G. A. Olah*: Friedel-Crafts and Related Reactions. Wiley, New York 1964, Vol. 3, pp. 1319ff., and further references cited therein.

[4] *W. R. Gaythwaite*, *J. Kenyon*, and *H. Phillips*, J. Chem. Soc. *1928*, 2283.

Table 1. Dehydrotropinones *(3a)*—*(3f)* from pyrroles *(1a)*—*(1e)* and α,α'-dibromo ketones *(2a)* and *(2b)*.

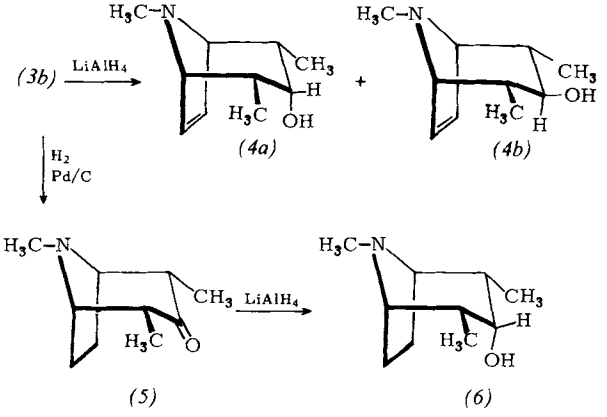
	(1)				(2)			Dehydrotropinone *(3)* [a]
	R^1	R^2	R^3		R^4	R^5		Yield [%] [b]
(1a)	H	H	H	*(2a)*	CH_3	H	*(3a)*	65 [c]
(1b)	CH_3	H	H	*(2a)*	CH_3	H	*(3b)*	89
(1b)	CH_3	H	H	*(2b)*	CH_3	CH_3	*(3c)*	70
(1c)	H	CH_3	H	*(2a)*	CH_3	H	*(3d)*	66
(1d)	CH_3	CH_3	H	*(2a)*	CH_3	H	*(3e)*	74
(1e)	H	CH_3	CH_3	*(2a)*	CH_3	H	*(3f)*	50

[a] The equatorial methyl protons resonate at δ = 0.90 ppm, axial methyl protons at 1.25 ppm, bridgehead methyls at 1.3 ppm and olefinic methyl protons at 1.61 ppm. The structural assignments are corroborated by comparison with model compounds [1] and by ^{13}C-NMR as well as IR spectra. Excellent microanalytical data were obtained for the crystalline hydrochlorides.

[b] Estimated by ^{1}H-NMR spectroscopy.

[c] The product contains the isomeric 2β,4β-dimethyl-8-azabicyclo[3.2.1]oct-6-en-3-one as the minor product in a ratio of 1:6.

The new route to tropinones complements the classical Robinson-Schöpf reaction[2]. A wide range of alkylated dehydrotropinones and nortropinones has become accessible, which can be converted into tropine analogs by conventional methods[3]. For example, reduction of *(3b)* with $LiAlH_4$ in ether yields 2α,4α-dimethyl-6,7-dehydrotropine *(4a)* and 2α,4α-dimethyl-6,7-dehydropseudotropine *(4b)* in equimolar amounts. In contrast, hydrogenation of the olefinic double bond [*(3b)*→*(5)*]



followed by $LiAlH_4$ reduction furnishes 2α,4α-dimethyltropine *(6)* with little (< 5%), if any of the corresponding pseudotropine isomer.

Experimental

In a typical experiment the dibromo ketone (0.01 mol) and redistilled or recrystallized (substituted) pyrrole (0.012 mol) in anhydrous acetonitrile (20 ml) are added dropwise over a period of *ca.* 30 min to a suspension of finely powdered copper (1.9 g, 0.03 mol) and sodium iodide (6.0 g, 0.04 mol) in acetonitrile (30 ml) under nitrogen. Efficient stirring is maintained at room temperature until all the dibromoketone has disappeared (usually 3 to 4 h). The mother liquor is worked up without delay by addition of dichloromethane (20 ml) and ice-cold water (200 ml), filtration from cuprous iodide and residual copper and washing with a little dichloromethane. After a further extraction of the aqueous filtrate with dichloromethane (50 ml) the combined organic layer is freed from any remaining copper by treatment with dilute ammonia until the blue color of the ammonia complex has completely disappeared. After drying with anhydrous sodium carbonate and removal of the solvent the resulting crude dehydrotropinone is purified by careful extraction with ice-cold dilute hydrochloric acid, neutralization at 0 °C and re-extraction into dichloromethane.

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[1] See also *H. M. R. Hoffmann*, Angew. Chem. *85*, 877 (1973); Angew. Chem. internat. Edit. *12*, 819 (1973); *H. M. R. Hoffmann* and *A. E. Hill*, Angew. Chem. *86*, 127 (1974); Angew. Chem. internat. Edit. *13*, 136 (1974).

[2] *R. Robinson*, J. Chem. Soc. *1917*, 762, and subsequent papers; *C. Schöpf*, Angew. Chem. *50*, 779 (1937); see in particular p. 783.

[3] Review of tropane alkaloids: *G. Fodor* in *R. H. F. Manske*: The Alkaloids. Academic Press, New York 1971, Vol. 13, Chapter 8.

Macromolecular Colloquium

The Macromolecular Colloquium was held at Freiburg (Germany), March 7—9, 1974. It was organized by the Institute for Macromolecular Chemistry of Freiburg University.

From the lectures:

A Contribution to the Thermodynamics of the Structural Transition of Phenylalanine-Specific Transfer Ribonucleic Acid in Solution

By *Th. Ackermann* (lecturer), *D. Bode*, *M. Grubert*, and *U. Schernau*[*]

With the physico-chemical investigation of solutions of a phenylalanine-specific transfer ribonucleic acid ($tRNA^{Phe}$) as an example, it is shown that important clues to the secondary and tertiary structure of dissolved biopolymers can be obtained from the temperature dependence of the thermodynamic variables of state. Conclusions regarding the "cooperativity" of the system can be drawn from the transition curves obtained by calorimetric and spectroscopic methods for a thermal denaturation process that is similar to the helix-coil transition. This cooperativity is strongly dependent on the composition of the solvent. The dependence on the concentration of Mg^{2+} ions is particularly pronounced. The accurate determination of the thermodynamic parameters of the system allows a comparison with the thermal reference values obtained by systematic investigations on nucleic acids and simple polyribonucleotides.

The minimum number of "base pairs" present in the secondary structure of the dissolved $tRNA^{Phe}$ can be estimated on the basis of these results. The result of this estimation is compared with the various models proposed in the literature (*e.g.* cloverleaf structure) for the secondary and tertiary structures of the dissolved phenylalanine-specific transfer ribonucleic acid.

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Applications of Neutron Scattering to Polymer Characterization

By *Henri Benoît*[*]

Neutron scattering will become a very important tool for studying polymers in solution and in bulk for two reasons: First, the wavelength of cold neutrons is of the order of 10 Å, thus facilitating determination of radii of gyration and of the whole scattering envelope; secondly, hydrogenated and deuterated samples differ greatly in their scattering intensity. Hence material can be studied in bulk, using normal polymer as the solvent and deuterated molecules as scattering objects.

Present and possible future applications of neutron scattering include: 1) size determinations on macromolecules in the glassy state and 2) in concentrated solutions; 3) effect of orientation and stretching on dimensions; and 4) conformation of copolymers.

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Polypivalolactone

By *Norbert Volkommer* and *Gerhard Bier* (lecturer)[*]

Pivalolactone and its preparation, polymerization, and use in particular as a fiber raw material have been the objects of numerous patents in recent years.

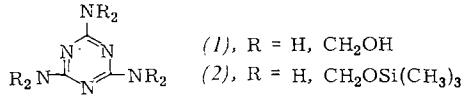
The syntheses of the monomer are briefly discussed. The monomer is advantageously polymerized with anionic initiators. The polymer, an aliphatic polyester with methyl side groups, is highly crystalline and has a melting point above 200 °C. The product can be processed thermoplastically.

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Structure of the Reaction Products of Melamine and Formaldehyde

By *D. Braun* (lecturer) and *V. Legradic*[*]

The first stage in the reaction between melamine and formaldehyde in aqueous alkaline medium yields mixtures of mono- to hexakis(hydroxymethyl)melamine *(1)*.



(1), R = H, CH_2OH
(2), R = H, $CH_2OSi(CH_3)_3$

The melamines *(1)* were converted into the silyl ethers *(2)* by reaction with *N,N*-diethyltrimethylsilylamine. By gel-chromatographic fractionation followed by careful hydrolysis, it was possible for the first time to isolate the hydroxymethylmelamines *(1)* preparatively and to establish their structure by analysis and by IR and NMR spectroscopy.

In addition to the hydroxymethylation, the initial phase also involves condensation to form oligomers with several melamine nuclei, which can also be separated by gel chromatography. Since equilibria are always established between bound and free formaldehyde in aqueous reaction solutions of melamine and formaldehyde, the *N*-hydroxymethyl groups of the condensates can be removed by reaction with ammonia to form hexamethylenetetramine; hydroxymethyl-free polynuclear compounds are then left behind. In the condensates prepared in the presence of alkali, the melamine residues are linked mainly *via* methyl ether bridges.

In addition to melamine resin, polyoxymethylene glycols are also formed from formaldehyde in aqueous medium; these can also be detected by gel chromatography and are present in the industrial products.

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Synthesis and Some Properties of Star Polymers with more than 100 Branches

By *H. Eschwey*, *M. L. Hallensleben*, and *W. Burchard* (lecturer)[*]

Three fundamental methods, all involving anionic polymerization have been described for the preparation of polymers branched in the shape of a star:

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1) Termination method:

Linear living polymers with relatively uniform molecular weight distributions and a carbanion end group are allowed to react with polyfunctional terminators containing halogen, such as $SiCl_4$. In this method the halogen atoms are replaced by the living polymer chains.

2) Propagation method:

The anionic polymerization is initiated with the aid of polyfunctional initiators, which initiate the growth of several polymer chains simultaneously from a common center. Living star polymers are obtained.

3) *Rempp*'s method:

Linear living polymers with a carbanion end group are copolymerized anionically with a small quantity of a bifunctional monomer, *e.g.* living polystyrene with divinylbenzene. The products consist of small, internally crosslinked polydivinylbenzene nuclei with long pendant polystyrene branches.

Methods 1 and 2 have so far been confined to the synthesis of star polymers with 3—6 branches. Star polymers with at most 20 branches can be obtained by method 3.

We have developed another method in order to obtain polymers with more branches and higher molecular weights. In this method, polyfunctional macromolecular initiators (soluble living polydivinylbenzene microgels of different sizes and with different numbers of carbanion groups that are active in the polymerization) were prepared by anionic polymerization. When these initiators were used as initiators for the anionic polymerization of styrene, they allowed the synthesis of star polymers having from 8 to about 400000 branches and molecular weights of 10^3—10^9. The products were characterized by means of light scattering and viscometry. The g' factor showed pronounced deviations from the Zimm-Kilb theory for star polymers. The shape factor of the light scattering is in good agreement with theoretical calculations.

^{1}H and ^{13}C Relaxation Measurements on Homopolymers and Copolymers

By *W. Gronski, R. G. Brüssau,* and *H.-J. Cantow* (lecturer)[*]

Chain movement, steric hindrance, and intramolecular interaction of the phenyl groups were investigated for solutions of polystyrene and copolymers of styrene (ST) with maleic anhydride (MAH), vinyl chloride (VC), and butadiene (BU). These investigations were carried out by determination of the spin-lattice relaxation times of ^{1}H and ^{13}C nuclei having different chemical shifts with the aid of the Fourier transform technique.

The temperature dependence of the ^{13}C relaxation of atactic polystyrene in D_8-dioxane gives an activation energy of 4.5 kcal/mol for the chain motion. The temperature dependence shows no significant difference for atactic and for isotactic polystyrene. The contribution of the intramolecular interaction of the side groups to the relaxation of the phenyl protons can be isolated from ^{1}H relaxation measurements on partly deuterated polystyrenes. By additional use of the correlation time of the chain movement as determined from the ^{13}C relaxation, it is thus possible to establish the conformation of the phenyl rings.

The ^{1}H and ^{13}C relaxation times of the styrene units in alternating ST-MAH copolymers are considerably shorter than in polystyrene; this is a consequence of the reduced mobility of these copolymers. Similar behavior is found for ST-VC copolymers: the relaxation time decreases with increasing length of the VC sequences.

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On the other hand, the chain mobility of ST-BU copolymers is so great that the ^{13}C relaxation times of the phenyl ring in a concentrated solution (65 wt.-%) of a random copolymer with a styrene content of 25 wt.-% are about five times as long as in a 20% polystyrene solution. The correlation time of the segment motion of styrene units at 52 °C is 1.4×10^{-10} s. The steric hindrance of the side groups is so slight that the rotation of the rings can be detected. The correlation time for the rotation is about 2.5 times as long as that for the segment motion.

Mechanism of the Degradation of Polymers in Solution by Ultrasound

By *A. Basedow* and *K. H. Ebert* (lecturer)[*]

The degradation of polymers in solution by ultrasound has been investigated in the molecular weight range from 30000 to 100000. The degradation products were characterized by determination of the molecular weight distributions with the aid of chromatography on porous glass.

In the discussion of the numerous results, it is not possible to say *a priori* whether the degradation reaction is caused by shock waves or by inhomogeneous flow fields. Investigations on the degradation kinetics of dextran in various solvents and with the addition of third substances show that the nature of the solvent has a considerable influence on the cavitation characteristics, and hence also on the degradation constants, since the cavity implosion energy determines the intensity of the shock waves or inhomogeneous flow fields produced. A quantitative relation has been found between the molar enthalpy of vaporization of the solvent and the degradation constant. The influence of solvation and hence of the solvent-polymer interaction on the degradation reaction is only slight. However, our results indicate that expansion of the polymer coil favors degradation. According to the existing theoretical views this means that the rupture of the molecules is caused mainly by shock waves. The experimental observation that the molecules disintegrate into two parts of approximately equal size suggests that the inhomogeneous flow fields cause stretching of the polymer coils; rupture may occur in this way in the high molecular weight range.

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^{13}C-NMR Spectroscopy on Polyethers

By *D. Fleischer* (lecturer) and *R. C. Schulz*[*]

The chemical and physical properties of many copolymers exhibit characteristic variations with the distribution of their monomer units. If this sequence distribution is known, it is possible to draw conclusions regarding the mechanism of the polymerization reaction. The investigations on this point and the determination of the overall composition were carried out by ^{13}C-NMR spectroscopy on polymers that had been obtained by polymerization of oxacyclic monomers (ethylene oxide, 1,3-dioxolane, 1,3,5-trioxane, 1,3,5-trioxepane, and 1,3,6-trioxocane) with ring cleavage and consisted only of methylene oxide (M) and ethylene oxide (E) units.

^{1}H-NMR spectra of these homopolymers and copolymers show triad sequences for the M units, whereas only one practically unresolved signal is observed for the E units in every case. With the aid of the greater chemical shift in the ^{13}C-NMR

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spectrum it is possible to distinguish EE linkages from isolated E units in MEM triads, and the nature of the ring cleavage can thus also be easily determined in this way.

However, greater sequence lengths can also be determined by ^{13}C than by ^{1}H-NMR spectroscopy, and can even be quantitatively determined because of approximately equal relaxation times. Thus pentad sequences have been found both for the M and for the E units. These results enable conclusions to be drawn with regard to the side reactions that accompany the growth reactions.

Finally, by the use of europium chelates as shift reagents, it is possible to assign heptad sequences to the resonance lines, and these sequences can also be quantitatively determined.

New Methods for the Preparation of Reactive Microgels and Their Use for the Construction of Inhomogeneous Networks

By *W. Obrecht*, *U. Seitz*, and *W. Funke* (lecturer)[*]

Microgels with pendant reactive vinyl groups were prepared by polymerization and copolymerization of divinyl and dimethacrylic monomers. A new method was developed for the purification of the emulsion polymers; it was possible to isolate the microgel particles in a highly dispersed form by this method.

The size and size distribution of the resulting polymers were determined (by electron microscopy), as well as the number of pendant double bonds (by several addition reactions).

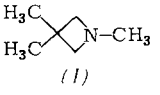
By copolymerization of reactive microgels with bifunctional monomers, networks with a defined inhomogeneous structure could be prepared.

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Cationic Polymerization of Azetidines

By *E. J. Goethals* (lecturer) and *E. Schacht*[*]

1,3,3-Trimethylazetidine *(1)* and azetidine *(2)* are quantitatively converted into polymers above 60 °C by cationic initiators. The polymerization of *(1)* was investigated with nitrobenzene as the solvent and triethyloxonium tetrafluoroborate as the initiator.



(1)



(2), R = H

(3), R = $(CH_2)_3NH_2$

Kinetic measurements and investigations by 300-MHz ^{1}H-NMR spectroscopy showed that the growing chains in this polymerization are cyclic quaternary ammonium salts, and that the concentration of the growing chains remains constant in the course of the polymerization. The absence of a termination reaction between growing chains and polymeric amino groups is explained by the fact that the basicity of the monomer is much greater than that of the polymer.

The polymerization of azetidine *(2)* was investigated in methanol with perchloric acid as the initiator. A dimer *(3)* is first formed in a high yield from *(2)*. This dimer polymerizes further to give a polymer in which 20% of the amino groups are tertiary, 60% secondary, and 20% primary.

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Polycondensation of *N*-Silylated Bis-Amides and Bis-Imides

By *W. Keller* and *G. Greber* (lecturer)[*]

The reactions of *N*-trimethylsilylated amides, imides, and ureas with active halogen compounds, which proceed with elimination of trimethylchlorosilane, have been investigated with regard to the possible use of this reaction for the preparation of polymers. By polycondensation of bifunctional *N*-trimethylsilylated amides, imides, and ureas with dichlorides of dicarboxylic acids or with *o,m,p*-xylylene dihalides, a series of polymers with new structural elements have been prepared and characterized.

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Proton Resonance Measurements on Polymaleic Anhydride and Maleic Anhydride-Isobutene Copolymers

By *D. O. Hummel* (lecturer) and *J. Bestgen*[*]

The compositions and configurations of a series of maleic anhydride(MA)-isobutene(IB) copolymers (produced by radiation chemistry) and the structure of homopolymeric polymaleic anhydride (PMA) were investigated by ^{1}H-NMR spectroscopy.

The nature and frequency of occurrence of the sequences were determined for the MA-IB copolymer. On the other hand, resolution of the PMA resonance complex into individual lines and hence an assignment to specific *n*-ads is impossible, since PMA is a complicated multispin system with small chemical shifts.

Comparison of spectra of several samples with different monomer concentrations in the starting mixture provided evidence of equimolar alternance of the copolymer.

With the aid of the Karplus theory and on the basis of values of coupling constants for model substances, the determination of the coupling constants of the methine protons led to the result that only *trans* opening of the double bond in MA occurs on addition of the IB monomers; the MA units in the chain consequently have the *threo* configuration. Strong steric hindrance of the *cis* opening is assumed in order to explain this.

A resolution of the methyl resonance led to two doublets with different intensities, which can be assigned to *threo*-diisotactic and *threo*-disyndiotactic linkages of the MA units, the diisotactic orientation being slightly favored over the disyndiotactic.

No differences in configuration were found for samples that had been polymerized at different temperatures and in different solvents.

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Macrozwitterions

By *W. Kern* (lecturer), *V. Jaacks* (deceased), and *H. Schnecko*[*]

Macrozwitterions[1] have a positive charge at one end of the linear oligomeric or polymeric molecule and a negative

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charge at the other. They are thus true zwitterions, and can form salts with corresponding counterions.

Macrozwitterions are interesting in two respects:

1) as themselves, because the conformation of the charge carrier can be studied as a function of the distance between the opposite charges and as a function of the medium; and

2) as intermediates in certain ionic polymerizations.

Some strongly polar monomers polymerize cationically with ansolvo acids, and other polar monomers polymerize anionically with ansolvo bases. However, it is not easy to choose the reaction conditions so accurately that one can say that there is no cocatalyst (*e.g.* H_2O) present. Even in very small quantities, water reacts with the Lewis acid or the Lewis base to form a protonic acid that initiates a cationic polymerization or a hydroxide-ion base that initiates an anionic polymerization.

However, if it can be shown that macrozwitterions with provable structures occur in polymerization mixtures where proton-active compounds have been ruled out as far as possible, conclusions can be drawn with regard to the mechanism of this polymerization, *i.e.* a zwitterion mechanism can be deduced. No macrozwitterions can occur in cocatalysis.

Tertiary phosphanes initiate the anionic polymerization of acrylonitrile and are incorporated as phosphonium ions. Some cyclic compounds can also be polymerized with simultaneous ring cleavage by ansolvo compounds to give macrozwitterions, *e.g.* β-lactones with the aid of tertiary amines. Reactions of this type are very suitable for the synthesis of macrozwitterions.

[1] *K. Boehlke, M. J. Han, V. Jaacks, N. Mathes,* and *K. Zimmerschied,* Angew. Chem. *81*, 336 (1969); Angew. Chem. internat. Edit. *8*, 386 (1969).

Quasi-Static Glass Temperature and Configuration Entropy

By *H. G. Kilian*[*]

The states at the quasi-static glass temperature of homologous polymer systems apparently have the same free volume. If this limiting state is regarded as a liquid saturated with holes (with a hole size distribution), it can be shown by the thermodynamic description of known measurements on homologs of polystyrene and on polystyrene-solvent mixed systems that regardless of the molecular structure of the liquid, an "iso-excess entropy state" probably exists at T_g'. Holes, polymer molecules, and solvent molecules evidently do not have a random arrangement, but are distributed in such a way that the deviations from the ideal athermic mixture at $T_{g\infty}$ are the same for all the systems investigated.

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Structure of Macromolecular Adsorption Layers on Solids

By *E. Killmann* (lecturer), *M. v. Kuzenko, H. J. Strasser,* and *K. Winter*[*]

The elucidation of the conformation of adsorbed macromolecules is the aim of investigations on polymer adsorption from solution on solid surfaces. In addition to the adsorbed amount (obtained from the difference between the concentrations of the polymer solution before and after adsorption) the thickness and concentration of the adsorbed layer (ellipsometrically), the enthalpy of adsorption and of immersion (calorimetrically), and the number of adhesive segments per macromolecule (IR spectrometrically) were determined.

The results obtained by these methods for layers of polyethylene glycol, polystyrene, and polyvinylpyrrolidone adsorbed on Aerosil (SiO_2) and chromium surfaces from various solvents are compared. The dependences of the characteristic parameters on the concentration, the molecular weight and the kind of polymer, on the kind of solvent and on the state of the adsorbent surface lead to conclusions about the structure of the adsorbed layer and its dependence on the degree of coverage, the competing interactions in the polymer-solvent-adsorbent system, and the size and shape of the macromolecule in solution.

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Synthesis of Alternating Copolyamides and their Sequence Analysis by ^{1}H- and ^{13}C-NMR Spectroscopy[1]

By *H. R. Kricheldorf* (lecturer), *E. Leppert,* and *G. Schilling*[*]

The monomers *(1)*—*(3)* were synthesized from silylated aromatic or aliphatic ω-amino carboxylic acids. All three classes of monomers can be polycondensed in solution to form copolyamides with alternating sequences. However, temperatures of 180—250 °C are necessary for the condensation of *(1)* and *(2)*, and the best results are therefore obtained by condensation in the melt in these cases.

$$C_6H_5O\text{–}CO\text{–}NH\text{–}A\text{–}CO\text{–}NH\text{–}B\text{–}COOH \quad (1)$$

$$S{=}C{=}N\text{–}A\text{–}CO\text{–}NH\text{–}B\text{–}COOH \quad (2)$$

$$CF_3\text{–}COO^{\ominus}\,[\overset{\oplus}{N}H_3\text{–}A\text{–}CO\text{–}NH\text{–}B\text{–}COOC_6Cl_5] \quad (3)$$

A, B = bivalent aliphatic or aromatic residue

For copolyamides of *p*-aminobenzoic acid and aliphatic ω-amino carboxylic acids, the sequence can be checked with the aid of ^{1}H-NMR spectra, and specifically the signals of the aliphatic protons. The resolution of the ^{1}H-NMR spectra is no longer sufficient in the case of purely aliphatic copolyamides, but homologous and alternating sequences can be distinguished by means of the carbonyl C signals of the ^{13}C-NMR spectra. These sequence analyses have shown that transamidation reactions disturb the alternating sequences at condensation temperatures > +200 °C.

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[1] For more detailed papers see: Die makromolekulare Chemie, in press.

Structural Investigations on Fibrinogen in Solution

By *K. Lederer* (lecturer), *R. Hammel,* and *J. Schurz*[*]

We have investigated solutions of fibrinogen ($c = 3$—20 g/l) by X-ray small angle scattering and viscometry. At very small angles the X-ray small angle scattering showed a strong dependence on the preparation of the sample, while the data normalized to the unit of concentration exhibited very little concen-

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[1] *L. Buchmann, W. W. Schmitt-Fumian, R. Hammel,* and *K. Lederer,* to be published.

tration dependence. These disturbances, which were due to aggregates, were largely eliminated on filtration of the solutions. The X-ray small angle scattering measurements on the filtered solutions gave a value of $R = 122$ Å for the radius of gyration, a molecular weight of $M = 335000 \pm 25000$, and $R_q = 24$ Å for the cross section radius of gyration, from which a length of $L = 430$ Å can be deduced on the assumption of a rod-shaped fibrinogen molecule. On the other hand, the viscosity measurements at a rate of shear $q = 10^4$—$5 \times 10^5\ s^{-1}$ gave a very low pseudoplasticity, which, on the basis of the value $D_{Rot} = 40000\ s^{-1}$ for the rotational diffusion constant from flow birefringence measurements, points to an axial ratio $p \leqslant 5$.

These results and earlier results reported by other workers may be compared with the calculated properties of fibrinogen models. The best agreement of all data was obtained on assumption of a sausage shape for the fibrinogen molecule, with a length $L = 450$ Å and a thickness $2R = 90$ Å, as suggested by *Bachmann, Schmitt, Hammel,* and *Lederer*[1] on the basis of electron micrographs of preparations obtained by the spray freeze etching method. The large volume of this model ($V = 3 \times 10^6$ Å^3) gives a hydration of about 5 g of H_2O/g of fibrinogen, which is unusually high for proteins. It is feasible that the highly swollen structure of fibrinogen possesses considerable flexibility.

Matrix Polymerization of Methyl Methacrylate

By *T. Miyamoto* (lecturer), *S. Tomoshige*, and *H. Inagaki*[*]

Recently it has been demonstrated that under some specific conditions, stereospecific polymerization of methyl methacrylate (MMA) may proceed through a reaction mechanism in which the stereocomplex formation plays an essential role. The stereocomplex consists of a mixture of isotactic and syndiotactic polymethyl methacrylate (PMMA), and is contained in the acetone-insoluble fraction.

This report deals with some specific features of PMMA prepared with *n*-butylmagnesium chloride in toluene at -50 °C. For the purpose of experiment, we have developed a new preparative technique to separate the stereocomplexes into components. The principle of this technique consists in competitive adsorption of two different tactic polymers from solution onto the surface of an adsorbent such as silica gel (solvent: chloroform).

The acetone-insoluble fractions of the products obtained by the polymerization in the absence of preformed PMMA (blank polymerization) were separated successfully into isotactic and syndiotactic components on a preparative scale by our technique. The content of isotactic triads in isotactic components was remarkably high (*ca.* 85 %), while the content of syndiotactic triads in syndiotactic components was *ca.* 60—70 %. The molecular weight of syndiotactic components was considerably lower than that of isotactic components. Furthermore a relation was found between the steric structure of whole polymerization products and the conversion of monomer; the products obtained at lower conversions (< 10 %) were predominantly isotactic, and with increasing conversion the isotacticity decreased to a constant value. On the other hand, the acetone-soluble fractions were assigned as "atactic" from their behavior on thin layer chromatography.

The polymers obtained in the presence of preformed isotactic PMMA (matrix polymerization), in sharp contrast with the products obtained by blank polymerization, were predominantly syndiotactic, especially when the ratio of amount of produced polymer to added polymer was lower than *ca.* 2. No exact parallelism between the molecular weights of added and produced polymers could be confirmed.

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Synthesis of Macromolecules of Well Defined Properties by Enzymatic Polycondensation

By *B. Pfannemüller*[*]

The kinetics of the phosphorylase-catalyzed polycondensation of glucose-1-phosphate to form α-(1→4)-glucan (amylose) with maltotetraose and higher oligomers as primer are analogous to the kinetics of the anionic polymerization with butyllithium. The primer in the phosphorolytic synthesis corresponds to the initiator in the anionic polymerization. However, the monomer is activated in the enzymatic polycondensation, whereas the growing chain is activated in the anionic polymerization.

As in the anionic polymerization, the linear synthetic product exhibits the following characteristics: 1) regulation of the degree of polymerization by the primer concentration and the conversion ($DP = 4$—approx. 30000); 2) high homogeneity ($P_w/P_n = 1.001$—1.01)[1]. Moreover, the enzymatically synthesized product: 3) is a stereoregular polymer capable of forming a helical structure[2]; and 4) it contains functional groups and can be investigated in *aqueous* media and in organic solvents (as derivatives).

As in the anionic polymerization, block polymers of ABA type can also be obtained by phosphorolytic polycondensation.

Anionic polymerization of macromolecules with more than two *living* ends has only recently been achieved[3], and star-shaped polymers have been synthesized so far mostly by a termination method. However, polymers with numerous growing chains are readily prepared by enzymatic synthesis.

Living comb-shaped polymers are obtained by coupling the primer molecules chemically to side groups of an existing linear chain. Glycoside linkages, alkali-labile ester linkages, and acid-labile hydrazone linkages have been studied for this purpose. Polysaccharides and polyacrylamide are used as carrier molecules. Corresponding experiments have been carried out also with cyclodextrin and polyfunctional benzene derivatives.

Using glycogen and amylopectin as polyfunctional primers star polymers having 15—20 and 10000 chains respectively per molecules are obtained. The problem of determination of the number and lengths of the new chains is discussed.

Amylose in aqueous solution exhibits an association tendency with an unusual chain length dependence. This property appears to be even more pronounced in some branched products. The linear amylose molecules are known to be capable of forming a helical superstructure. It is found by measurements of the ORD and CD spectra that the capability for helix formation persists even in highly branched products.

The fibril formation observed with the linear amylose-iodine complexes on examination in the electron microscope enables the star-shaped structure to be imaged directly.

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[1] *B. Pfannemüller and W. Burchard*, Makromol. Chem. *121*, 1 (1969).

[2] *B. Pfannemüller, H. Mayerhöfer*, and *R. C. Schulz*, Biopolymers *10*, 243 (1971).

[3] *H. Eschwey, M. L. Hallensleben*, and *W. Burchard*, Makromol. Chem. *173*, 235 (1973).

Structure and Properties of Pharmacologically Active Polymers

By *J. Bartulin, H. G. Batz, G. Franzmann, V. Hofmann, M. Przybylski, H. Ringsdorf* (lecturer), and *H. Ritter*[*]

Pharmacologically active macromolecular compounds, which are still regarded with skepticism for theoretical and practical reasons, have attracted growing interest during recent years because of their polymer-specific properties[1].

For low molecular weight drugs, a change in structure leads in most cases to a loss of specific activities. Vital properties of macromolecular drugs, on the other hand, depend on their polymeric structure, which can be relatively easily influenced *e.g.* by comonomers, polymer-analogous reactions, and crosslinking. A new model for pharmacologically active polymers takes into account *e.g.* possibilities for variation of their solubility and toxicity, the possibility of removal of the active groups (pharmacokinetics, depot effects), and the distribution of the polymers in the body[2]. In this connection, the synthesis[3] of macromolecular drugs and preliminary investigations on their activity are reported.

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65 Mainz, Johann-Joachim-Becher-Weg 18—20 (Germany)

[1] *K. P. Khomyakov, A. D. Virnik*, and *Z. A. Rogovin*, Russ. Chem. Rev. *33*, 462 (1964); *W. Kabaiwanow* and *M. Georgiewa*, Plaste Kaut. *19*, 886 (1972).

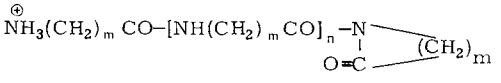
[2] *V. Hofmann*, Diplomarbeit, Universität Mainz 1973; *H. G. Batz, V. Hofmann*, and *H. Ringsdorf*, Makromol. Chem. *169*, 323 (1973).

[3] *G. Franzmann*, Diplomarbeit, Universität Mainz 1972; *H. G. Batz, G. Franzmann*, and *H. Ringsdorf*, Makromol. Chem. *172*, 27 (1973).

Mechanism of Cationic Polymerization of Lactams

By *M. Rothe* (lecturer), *G. Bertalan*, and *J. Mazánek*[*]

The kinetics and the mechanism of the cationic polymerization of ε-caprolactam and 8-octanelactam with anhydrous strong acids were investigated. Initiation results in the formation of the salt of the ω-amino acyllactam *(1)*, $n=0$; the chain growth takes place on the ammonium end group of this salt by transamidation with monomeric lactam or with acyllactam end groups. This yields polyamides with N-terminal ammonium groups and C-terminal *N*-acylated lactam rings *(1)*.



(1), m = 5, 7

Above 200 °C, subsequent reactions occur to an increasing extent on both end groups, and these reactions considerably alter the polymerization mechanism and the kinetics. N-Terminal amidine groups and acylamidine groups inside the chains are then formed; the water eliminated hydrolyzes the acyllactam and acylamidine groups to carboxyl groups.

The functional groups were determined in the same sample by potentiometric titration, acyllactam groups after hydrolytic conversion into carboxyl groups, and amidine residues after selective acylation of the amino groups. The concentrations of the groups depend on the polymerization conditions; amidine and carboxyl groups are present to a considerable extent even at the beginning of the polymerization.

Amidine groups initiate the polymerization of lactams much less effectively than amino groups; on the other hand, it is well known that they react very rapidly with carboxyl groups. Reactions of carboxyl groups with ammonium, amidinium, and lactam groups are therefore superimposed on the original growth-reaction.

The kinetic curves with their characteristic points of inflection can be explained by participation of these reactions.

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Some Problems and Results in Cellulose Research

By *G. V. Schulz*[*]

The following cellulose problems, which I started to investigate about 30 years ago together with Frau *E. Husemann*[1,2], are still topical today:

1) What is the molecular weight of native cellulose and what is its molecular weight distribution? 2) Does the cellulose molecule contain periodically arranged bonds that are easier to break ("weak points") or regions that are more susceptible to degradation ("weak zones")? 3) How are the chain molecules arranged in the fibrils?

The degree of polymerization of native cellulose appeared to grow continuously over the decades, until it was finally shown by investigations on cellulose from the bolls of cotton plants grown in a glasshouse that there are two kinds of cellulose: the primary wall cellulose, which has a very irregular structure, and a very uniform cellulose of the secondary wall, which has a degree of polymerization of about 14000[3,4]. Celluloses from other plants seem to correspond closely to this "model cellulose".

The other two questions can only be answered together. The earlier investigations indicated "weak points", separated by a regular distance of about 400—500 glucose units, in oxidative and hydrolytic degradation[1,5]. However, the starting materials were not native cellulose, since they had been modified by external influences after their biosynthesis. When we resumed the investigation of the oxidative degradation of native cellulose, we encountered the phenomenon of intramolecular crosslinking; this phenomenon greatly complicated the course of the degradation in time, and the molecular weight distributions[6]. The crosslinking effect shows that the cellulose molecules are folded in the native fiber; *Husemann et al.*[7] were able to show with greater certainty than before that the glucoside chains in the cellulose lattice have an antiparallel arrangement.

The kinetics of the degradation of cellulose can be quantitatively understood by reversal of a theory proposed by *Stockmayer*[8] for the polymerization of trifunctional and tetrafunctional monomers. According to this theory, unchanged native cellulose contains no bonds that are more readily broken by oxidation, and the molecular weight distributions correspond to those expected to result from purely random degradation. However, from the fact that the earlier results have been reproduced many times, it must be concluded that the "weak points", though produced by secondary effects, must be potentially present in the native cellulose molecule in view of their regular arrangement.

The above three questions now seem to be closer to a solution. The elucidation of these questions is an essential condition

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for the solution of the most interesting problem of all, *i.e.* that of the biosynthesis of cellulose in the plant.

[1] *G. V. Schulz* and *E. Husemann*, Z. Phys. Chem. (B) *52*, 23 (1942).

[2] *G. V. Schulz*, Z. Phys. Chem. (B) *51*, 127 (1942); *52*, 50 (1942).

[3] *M. Marx-Figini* and *G. V. Schulz*, Biochim. Biophys. Acta *112*, 81 (1966).

[4] *M. Marx-Figini* and *E. Penzel*, Makromol. Chem. *87*, 307 (1965).

[5] *E. Husemann* and *M. Göcke*, Makromol. Chem. *2*, 297 (1948); *4*, 194 (1949).

[6] *A. Palma, S. Jovanović*, and *G. V. Schulz*, Makromol. Chem. *169*, 219 (1973).

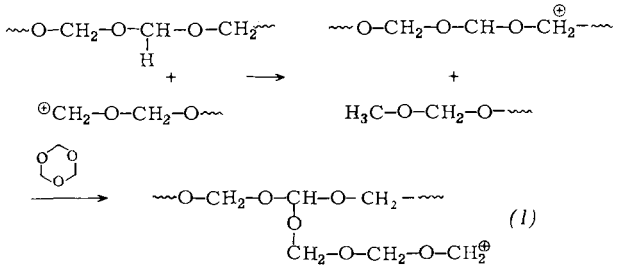
[7] *A. Kuppel, E. Husemann, E. Siefert*, and *P. Zugenmaier*, Kolloid-Z. Z. Polym. *251*, 432 (1973).

[8] *W. H. Stockmayer*, J. Chem. Phys. *12*, 125 (1944).

Occurrence of Branching Reactions in the Copolymerization of Trioxane with 1,3-Dioxolane

By *K.-H. Burg, H. Leugering*, and *G. Sextro* (lecturer)[*]

The formation of branched molecules *(1)* can be expected in principle in the homopolymerization of trioxane[1].



(1)

The detection of branched structures is particularly difficult because of the thermal instability of trioxane homopolymers; the situation is more favorable in trioxane copolymers. As far as we knew, however, branched structures had never been detected either for the homopolymers or for copolymers.

It is known that the spherulite size in polyoxymethylenes is very sensitive to traces of branched or crosslinked polyoxymethylenes[2], though there are at present no quantitative views on the mechanism of this nucleation process.

On the basis of the experimental findings, we then investigated copolymers of trioxane and 2 wt.-% of 1,3-dioxolane. The products were prepared and isolated under various conditions. On the basis of spherulite size determinations, experiments with model substances, and degradation experiments, it may be assumed that more than 99% of linear molecules are formed at polymerization temperatures of about 110 °C, whereas small quantities of branched chains are also obtained at 70 °C.

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[1] *W. Kern, H. Deibig, A. Giefer*, and *V. Jaacks*, Pure Appl. Chem. *12*, 371 (1966).

[2] *R. Kern, H. Schmidt, K.-H. Burg*, and *E. Wolters*, DOS 2101817 (1973), Farbwerke Hoechst.

Crosslinking Reactions in the Rubber Particles of High-Impact Polystyrene

By *H. Adler, G. Fahrbach*, and *D. J. Stein* (lecturer)[*]

The elasticity of the rubber phase in high-impact polystyrene is determined by the crosslink density, which thus has a decisive influence on the impact strength of the polymer. The rubber dissolved in styrene is crosslinked by reactions of its double bonds and allyl H atoms that take place simultaneously with the homopolymerization and graft polymerization of the styrene.

The suspension polymerization of solutions of rubber in styrene was investigated using several types of rubber, and with di-*tert*-butyl peroxide as the initiator. The following conclusions can be drawn from the results of the experiments: The preferred crosslinking point is the 1,2 configuration of butadiene. 1,4 and 3,4 configurations in butadiene and isoprene units also take part in the crosslinking reactions, but their reactivity is considerably lower. In butadiene-styrene copolymers the 1,2 configuration has roughly the same reactivity as in polybutadiene, but the reactivity appears to be lower in isoprene polymers. With all types of rubber, the crosslinking rate increases with increasing conversion of styrene; this is particularly noticeable at styrene conversions above 98%. This relationship is explained by a crosslinking copolymerization of the styrene with the 1,2 groups of the rubber.

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Peculiarities of the Particle Formation in the Emulsion Polymerization of Acrylic Esters

By *N. Sütterlin* (lecturer), *G. Markert*, and *H.-J. Kurth*[*]

Two approaches are generally used for the description of the particle formation in emulsion polymerization. The theory of *Smith* and *Ewart*[1] ascribes the decisive role to the micelles, whereas that of *Roe*[2] is based on a thermodynamic consideration of a dissolution-precipitation equilibrium. Both approaches lead *via* the same selection criteria to the same quantitative relations in the kinetics of the emulsion polymerization.

Practical experience has shown that the views of *Roe* are more probable. It is appropriate in this approach to pay greater attention to the equilibrium concentration of the monomers in the aqueous phase and at the same time to the hydrophilicity of the polymer.

If the mean number of particles per unit volume is plotted as a function of the soap concentration present at the start of the polymerization in logarithmic coordinates, one obtains the well-known S-shaped relations, in which the critical micelle concentration of the emulsifier is not a pronounced point of the curve. The number of particles for a given emulsifier concentration depends on the saturation concentration of the monomer in the aqueous phase.

The fact that the number of particles is substantially independent of the initial concentration of the emulsifier for very low and very high soap concentrations can be explained by agglomeration processes with different causes.

These agglomeration phenomena affect the mean number of particles in particular for the most hydrophilic members of the acrylate and methacrylate series. One reason for this is probably the equilibrium concentration of the emulsifier on the particle surface, which increases with increasing hydrophobicity of the polymer, with the result that more hydrophobic polymers are more effectively stabilized.

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[1] *W. V. Smith* and *R. H. Ewart*, J. Chem. Phys. *16*, 592 (1948).

[2] *C. P. Roe*, Ind. Eng. Chem. *60*, 20 (1968).

X-Ray and Calorimetric Detection of the Formation of Individual Kinks

By *A. Weiss* (lecturer), *G. Lagaly*, and *S. Fitz*[*]

Kinks and gauche blocks are postulated as the most important rotational-isomer forms of alkyl chains in crystalline and paracrystalline solids. We have been able to detect directly the formation of individual kinks on bimolecular layers of long-chain alkyl compounds and to determine the character of the transition and the transition enthalpies and entropies by measurement of the specific heat. In our model systems the kinks arrange themselves into blocks. Beyond a critical concentration, a drastic change in structure takes place with transformation into gauche block structures. The experimentally determined limiting concentrations of kinks for the kink block structures agree very closely with the values estimated by *Pechhold* and *Blasenbrey* from statistical thermodynamics.

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Conversions of Bacterial Polysaccharides by the Action of Lysogenic Phages and Their Immunochemical and Biochemical-Genetic Significance

By *O. Westphal*[*]

It is well known that the infection of species of Enterobacteriaceae with lysogenic phages leads to changes in the enzyme system for the biosynthesis of the corresponding specific bacterial (surface) polysaccharide, and hence to definite changes in the polysaccharide structure. The starting strain and the converted strain produce correspondingly different immune responses, *i.e.* antibodies with different specificities, in the animal. Details of the polysaccharide biosynthesis can be discovered by the biochemical study of lysogenic conversions, while immunochemical analysis allows a more precise definition of the polysaccharide structures that are responsible for the specificity, *i.e.* the determinant groups. Numerous enterobacterial species that have been known for a long time can be transformed into one another by lysogenic conversions. A picture of evolution mechanisms within bacterial genera is progressively emerging in this way. Lysogenic conversions exhibit analogies with some malignant transformations of cells in higher animals.

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Progress in the Synthesis of Human Proinsulin and of a Proinsulin Model

By *H. Zahn* (lecturer), *H. Berndt*, *J. Föhles*, *D. Brandenburg*, *W. Schermutzki*, and *V. K. Naithani*[*]

The chain of human proinsulin, which consists of 86 amino acid residues, is to be represented in the form of a monomeric cyclic tricystine peptide derivative with three disulfide bridges within the chain (A 6,7, A 11,20, and B 7,19). The thiol protection required for this was achieved by synthesis of the fragments B 1—B 23 with the cystine bridge B 7,19 and A 6—A 21 with the disulfide bridges A 6,7 and A 11,20. The peptide derivatives required from the regions B 24—C 15 and C 16—A 5, as well as the human C peptide, are also available; the condensation of fairly large fragments can thus be taken in hand.

The question (discussed by *Steiner*) whether the C peptide ensures the correct pairing of the cysteine residues by specific interactions with the A and B chains or whether the segment merely serves as a flexible connecting link to allow intramolecular formation of the disulfide bridges has been answered by recombination studies on semisynthetic $N^{\alpha A1}$—$N^{\varepsilon B29}$—bridged insulins, which showed that the second of the above possibilities is correct. The linkage of the α-amino group of the glycine A1 with the ε-amino group of the lysine B29 *via* an L,L-diaminosuberic acid bridge yields a crystallizable "clamp" insulin, which can be recovered again in yields of about 70% after reduction of the three cystine bridges.

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[VB 377 IE]
German version: Angew. Chem. 86, 448 (1974)

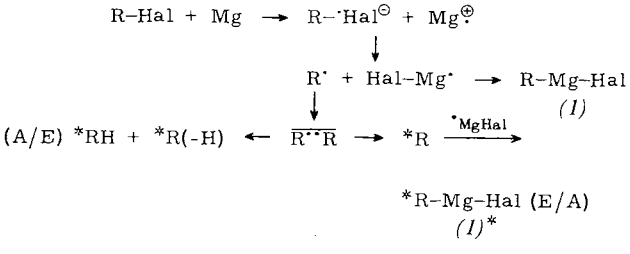
Free Radicals in Grignard Reactions

By *Friedrich Bickelhaupt*[*]

It has been suspected for some time that the formation of Grignard compounds *(1)* from alkyl halides and magnesium in ethers involves free radicals. Observation of the CIDNP effect in a Grignard reagent (*e.g. (1a)*; the relevant nuclei are emphasized in the formulas) has provided fresh direct evidence for the correctness of this assumption.

$$CH_3-CH_2-CH_2-I + Mg \xrightarrow{(n\text{-}C_4H_9)_2O} \underset{(1a)}{CH_3-CH_2-CH_2-MgI} \; (+\underset{(2a)}{CH_3-CH=CH_2} + CH_3-CH_2-CH_3)$$

The absence of a net effect and the occurrence of E/A polarization[**] in *n*-propylmagnesium iodide *(1a)* and of A/E polarization[**] in the side product propene *(2a)* support the following simplified reaction scheme[1]:



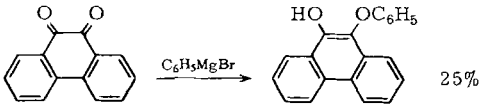
Both solvent effects and the behavior of 6-bromo-1-hexene, which readily undergoes cyclization to methylcyclopentane derivatives in the free radical state under the conditions of the Grignard formation reaction, constitute compelling evidence that the major reaction is direct combination of alkyl radical and magnesium(I) halide and that formation of polarized Grignard compound *(1)* via* the radical pair accounts for only a small percentage of the overall reaction.

Under certain conditions the occurrence of free radicals may also be expected in the reactions of Grignard compounds, *e.g.* in the reaction of *o*-quinones such as *(3)* with phenyl-

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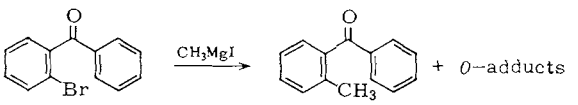
[**] For an explanation of the terms net effect, emission-absorption (E/A) polarization, and absorption-emission (A/E) polarization, see, *e.g.*: *S. H. Pine*, J. Chem. Educ. *49*, 664 (1972).

magnesium bromide, the phenyl radical adding to the oxygen of a carbonyl group[2]. The extent to which free radical intermediates participate in additions to simple ketones has yet to be established.



(3)

In the reaction of 2-bromobenzophenone *(4)* with Grignard compounds, *e.g.* methylmagnesium iodide, addition to the carbonyl group is accompanied by reaction of the σ complex formed from ketone and Grignard compound, *i.e.* nucleophilic



(4)

aromatic displacement of the bromine by methyl to give 2-methylbenzophenone[3], which certainly proceeds ionically.

Lecture at Dortmund on November 6, 1973 [VB 379 IE]
German version: Angew. Chem. 86, 382 (1974)

[1] *H. W. H. J. Bodewitz, C. Blomberg,* and *F. Bickelhaupt,* Tetrahedron *29,* 719 (1973).

[2] *C. Blomberg, H. H. Grootveld, T. H. Gerner,* and *F. Bickelhaupt,* J. Organometal. Chem. *24,* 549 (1970).

[3] *C. Jongsma* and *F. Bickelhaupt,* Rec. Trav. Chim. Pays-Bas *92,* 1143 (1973).

ABSTRACTS

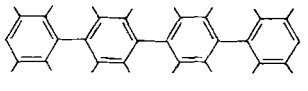
Reviews

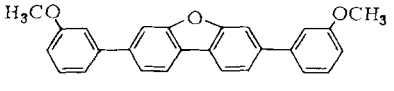
Abstracts of selected progress reports and review articles

The uses of chromium(II) salts in preparative organic chemistry are reviewed in an article by *J. R. Hanson.* They are used for the reduction of alkyl chlorides, unsaturated systems, epoxides, acyloxyketones, and nitro compounds. In addition to the chloride, sulfate, and perchlorate, a Cr(II)-ethylenediamine reagent has been found to be a very effective reducing agent. Certain solvents and H donors such as *n*-butanethiol or hypophosphorous acid can influence the course of the reaction. In several cases the use of Cr(II) salts permits selective reductions, *e.g.* the reduction of halides and nitro groups, whereby CO groups remain intact. [Applications of Chromium(II) Salts in Preparative Organic Chemistry. Synthesis *1974,* 1–8; 55 references]

[Rd 694 IE –M]

Novel applications of the Ullmann synthesis of symmetric and asymmetric biarylenes, biphenylenes, and ring compounds are described by *P. E. Fanta.* An arylcopper compound almost certainly functions as an intermediate in the synthesis. The reactivity of an aryl halide is strongly substituent-dependent: electronegative groups such as nitro and methoxycarbonyl groups, particularly in the *ortho* position, activate the halogen atom considerably; amino, hydroxy, and carboxy groups inhibit or impede the reaction, as do bulky groups in the *ortho* position. The Ullmann reaction has been applied to heterocyclic systems and the synthesis of oligoarylenes. The reaction of a large excess of a monofunctional component with a difunctional diiodo compound to give linear polyphenylenes is to be regarded as a cocondensation-Ullmann reaction. This method is particularly suitable for the synthesis of highly substituted and bridged polyphenylenes, such as *e.g. (1)* and *(2).* [The Ullmann Synthesis of Biaryls. Synthesis *1974,* 9–21; 145 references]


(1)



(2)

[Rd 695 IE –M]

Photodifluoroamination and reactions of fluorine atoms are reviewed by *C. L. Bumgardner* and *E. L. Lawton.* Tetrafluorohydrazine, N_2F_4, reacts with lower alkanes RH on irradiation with replacement of a hydrogen atom by the NF_2 group:

$$N_2F_4 \rightleftharpoons 2\,NF_2$$

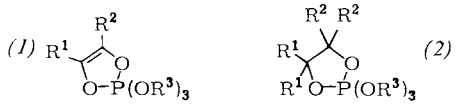
$$NF_2 \xrightarrow{h\nu} F + NF$$
$$RH + F \rightarrow R + HF$$
$$R + NF_2 \rightarrow RNF_2$$
$$R + N_2F_4 \rightarrow RNF_2 + NF_2$$
$$2\,NF \rightarrow N_2F_2$$
$$NF + NF_2 \rightarrow N_2F_2 + F$$

Methane yields not only CH_3NF_2 but also HCN, which is formed by unimolecular HF elimination. Both NF_2 and F can add to alkenes, *e.g.* propylene. In this system unimolecular elimination of CH_3 can also take place. On photodifluoroamination of propyne and allene rearrangements occur. Nitriles react in the same way as alkynes. [Photodifluoroamination and Atomic Fluorine Reactions. Accounts Chem. Res. *7,* 14 to 20 (1974); 33 references]

[Rd 697 IE—L]

Structure, syntheses, and reactions of oxyphosphoranes are reviewed by *F. Ramirez.* Oxyphosphoranes are compounds containing pentacoordinate phosphorus bonded to at least one oxygen atom: $(RO)_{5-n}PX_n$, $n = 0$—4. Their synthetic value has been realized during the past decade. Five-membered cyclic oxyphosphoranes are stable. The survey deals in particular with five-membered systems containing two endocyclic O atoms with one or no double bonds, with special reference to the chemical behavior of 2,2,2-trialkoxy-1,3,2λ⁵-dioxaphos-

pholes *(1)* and -phospholanes *(2)*. In addition, brief mention is made of other cyclic oxyphosphoranes, *e. g.* 2,2,2-trialkoxy-1,2λ^5-oxaphospholenes and $-\Delta^4$-1,4,2λ^5-oxazaphospholenes.



The synthesis of *(1)* and *(2)* from trialkyl phosphites is considered in detail; preparative examples are given. [Synthesis *via* Oxyphosphoranes. Synthesis *1974*, 90—113; 108 references]

[Rd 700 IE—M]

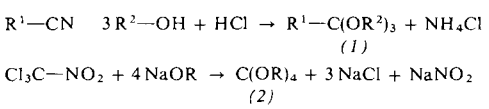
Progress in lithium chemistry in 1972 is surveyed by *W. H. Glaze*. A consideration of questions relating to structure and bonding, kinetics and reaction mechanisms is followed by a treatment of lithium carbenoids and halogen-substituted organolithium compounds. There follow lithiation reactions (H→Li exchange). A series of interesting publications is concerned with the use of lithium compounds as polymerization initiators, and for the after-treatment of polymers in order to modify their properties. Addition reactions of Li compounds to carbonyl compounds, olefins, and similar substrates, as well as reactions with heterocycles and with organometallic compounds close the review. [Lithium Annual Survey Covering the Year 1972. J. Organometal. Chem. *68*, 1—67 (1974); 233 references]

[Rd 705 IE—M]

The photochemical hydroxylation of aromatic compounds, which is, *inter alia*, of biological interest, is considered from a preparative viewpoint by *T. Matsuura* and *K. Omura*. The survey embraces direct hydroxylation with replacement of H by OH, hydroxylation with replacement of a substituent attached to an aromatic ring, and a number of other methods. Direct hydroxylation can be carried out with photochemically generated OH radicals, *e. g.* from Fenton reagent, from water by radiolysis, from dilute aqueous H_2O_2 solution by photolysis, and with atomic O (from N_2O, *N*-oxides of heterocyclic bases) as well as by dye-sensitized photooxygenation (*e. g.* tyrosine→dopa). The photochemical hydrolysis of aromatic diazonium salts, halides, and nitrobenzene derivatives affords phenols, the other substituents exerting a pronounced effect on the reaction course. [Photochemical Hydroxylation of Aromatic Compounds. Synthesis *1974*, 173—184; 63 references]

[Rd 701 IE—M]

Methods for the synthesis of orthocarboxylic esters *(1)* **and orthocarbonic esters** *(2)* are discussed by *R. H. DeWolfe*, paying special attention to the synthesis of acyclic representatives and heterocyclic orthoesters having 1,3-dioxolane, tetrahydrofuran, tetrahydropyran, 2,6,7-trioxabicyclo[2.2.2]octane, or 2,4,10-trioxaadamantane structures and spiro systems. Orthoformates *(1)*, $R^1 = H$, can be synthesized from HCN, formamide, trihalomethane, or halomethyl ethers, other orthoformates, or trithioorthoformates; orthocarboxylates *(1)* are accessible from nitriles, amidoyl chlorides, other orthoesters, ketene acetals, trihalomethyl compounds, and orthocarbonates. Orthocarbonic esters *(2)* are prepared from trihalomethyl compounds or halomethyl ethers, as well as by transesterification of tetramethyl orthocarbonate, and tetraalkyl orthocarbonates from dibutyltin dialkoxides and carbon disulfide.—Orthoesters are widely used in organic synthesis; cyclic orthoesters serve as valuable intermediates for the protection of hydroxy and carboxy groups. [Synthesis of Carboxylic and Carbonic Ortho Esters. Synthesis *1974*, 153—172; 143 references]

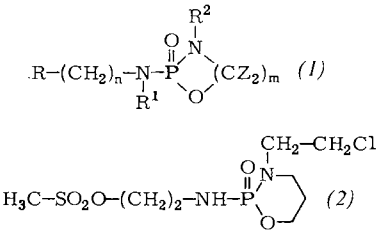


[Rd 702 IE—M]

Patents

Abstracts of selected "Deutsche Offenlegungsschriften" (DOS), *i. e.* provisionally published specifications as filed with the German Patent Office

Esters *(1)* of alkanesulfonic acids and 1,3,2-oxazaphospha cyclic alcohols have an immunosuppressive action and good

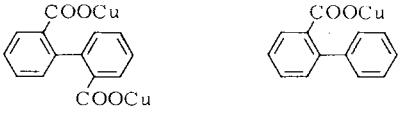


R = halogen, lower alkanesulfonyloxy
R^1, R^2 = H, alkyl(C_1—C_4), haloalkyl, lower alkanesulfonyloxy
Z = H, alkyl(C_1—C_4)
n = 2, 3

tolerance characteristics. They can be prepared by known methods. A preferred compound is *(2)*. [DOS 2107936; Asta-Werke AG, Brackwede]

[PR 158 IE—K]

In a new process for the production of diphenic acid and 2-phenylbenzoic acid, in which no starting materials obtained from coal tar are required, readily obtainable copper(I) phthalate is heated in a solvent (such as quinoline, pyridine, alkylpyridine) to 110 to 200 °C, and the copper(I) salts *(1)* and *(2)*



(1) *(2)*

are then separated and the free acids isolated. The ratio of *(1)* to *(2)* in the reaction mixture can be adjusted by means of the reaction temperature, higher temperatures giving larger proportions of *(2)*. [DOS 2214690; Aktiebolaget Bofors, (Sweden)]

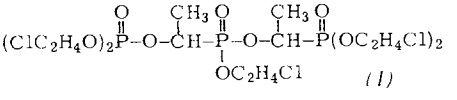
[PR 169 IE—U]

A process for increasing the molecular weight of high-density polyethylene in the polymerization of ethylene with methylated polysiloxanes, compounds of metals of the IVth subgroup, and aluminum chloride consists in the additional use of organotin compounds having the formula SnR_4. R may be identical or different aliphatic or cycloaliphatic residues. Even small quantities of tetrabutyltin mixed with the three components mentioned above cause a distinct increase in activity

and lead to a narrower molecular weight distribution with a remarkable increase in molecular weight (η_{red} 3—3.6 dl/g as compared with 2.13 dl/g). [DOS 2206386, Wacker-Chemie GmbH, München]

[PR 187 IE—W]

Combustion-resistant acrylic glass based on methyl methacrylate and phosphoric acid or esters of phosphoric acid are obtained by copolymerization with bromophenyl methacrylates (pentabromophenyl, dibromophenyl, and tribromo-



(1)

phenyl methacrylate). The softening point is only slightly depressed (Vicat values between 120 and 133 °C) by this addition. 5 to 10 wt.-% of *(1)*, phosphoric acid, or tris(bromocresyl) phosphate are used as the phosphorus derivative. [DOS 2202791, Röhm GmbH, Darmstadt]

[PR 188 IE—W]

Electrophoretic binders for cationic deposition that crosslink at high temperatures consist of a synthetic resin containing hydroxyl groups, which is partly allowed to react with a polyisocyanate blocked at one end, and also containing amino groups. The resin is dispersed in water by quaternization with lactic acid or acetic acid. As an example, a bisphenol A epoxy resin with an equivalent weight of 910 is allowed to react in *N*-methylpyrrolidine with a 2,4-toluene diisocyanate blocked at one end with 2-ethylhexanol, and dimethylamine is then added to react with the epoxide residues. The resin is dispersed with acetic acid in water. Binders that can be deposited cathodically offer improved protection against corrosion and do not attack phosphate protective films as readily as anionic binders. [DOS 2252536; PPG Industries, Inc., Pittsburgh, Pa. (USA)]

[PR 190 IE—W]

BOOK REVIEWS

Einführung in die Physik (Introduction to Physics). By *R. Fleischmann*. Verlag Chemie GmbH—Physik Verlag, Weinheim/Bergstr. 1973. 1st ed., xviii, 677 pp., 436 figures, 60 tables, bound DM 65.—.

This book, which is based on a series of lectures, resembles *Pohl*'s textbook in that it introduces and explains the essential physical concepts with the aid of briefly described experiments. Care is taken to distinguish clearly between quantities that should be kept conceptually separate, such as the inertial mass and the gravitational mass. This and other similar didactic measures may enable the author to achieve his aim of guarding the beginner (to whom the book is primarily addressed) as far as possible against the usual errors.

Special mention should be made here of the consistent references to the dimensions to be used and to the units, which are listed in a separate section at the end of the book. Here one also finds very useful tables for the conversion of units, for conversion to moving reference systems according to theory of relativity, for the mathematical use of scalars, of vectors and tensors, *etc.*

As far as the choice of subject matter is concerned, the book confines itself mainly to physical processes that can be approximately described and understood in terms of a mental picture. This does not mean, for example, that the wave nature of material particles is ignored, but the predominantly theoretical conclusion from wave and quantum mechanics (Schrödinger equation) play only a minor part in the book. In the field of thermodynamics, one of the concepts that are not easy to grasp and do not lend themselves to mental imagery is entropy; the discussions on this topic are probably not easy for the beginner to understand. On the other hand, there is a brief but nevertheless sufficiently informative description of the areas of physics that are vital to modern investigations in nuclear physics.

The physical laws are examined in the book with the aid of a variety of numerical examples. The examples unfortunately contain a number of discrepancies, which are particularly likely to trouble the student since he will probably assume that the values were obtained by some conversion or other, whereas they are actually simple errors of calculation. Discrepancies of this kind are also to be found in the tables, but these can easily be eliminated in a second edition.

Klaus Schäfer [NB 195 IE]

Boranes in Organic Chemistry. By *H. C. Brown*. Cornell University Press, Ithaca—London 1972, 1st ed., xiv, 462 pp., numerous figures, bound $ 24.50.

The new "H.C.B." is based on a series of lectures given at Cornell University in the autumn of 1969. The book is both more and less than its title suggests. Not only are the "Prolog" and the "Epilog" autobiographical in content, but the "life history" is also reflected by the choice of material and the emphasis in the presentation of all the other chapters. Thus the author's work on free radicals, steric effects, and (how could it be otherwise?) even on the problem of non-classical carbenium ions have been incorporated into the "boron book". Everything is considered from the view-point of the old campaigner. This is naturally also true of the actual "main" chapters, the "Selective Reductions", the "Hydroboration", and the "Organoboranes" and their reactions, among which the reactions with carbon monoxide, the alkylations, and free-radical reactions receive sections to themselves. The author's priorities are illustrated by the following example: The varied reaction of carbon monoxide with organoboranes, which has been dealt with by the author in numerous publications, is given 15 subsections with no fewer than 28 pages. The oxidation of organoboranes with *N*-oxides is not mentioned once in the entire book, though three sections covering 6 pages are devoted to the oxidations of the organoboranes.

The reader will derive special enjoyment and many a smile from numerous passages. The author expresses himself in so many places in his own characteristic manner. The descriptions of the ways in which results were achieved are interesting.

This will be useful to younger readers, particularly since such relationships usually cannot be found in the literature.

The book, which has a subject index and is otherwise excellently presented, is a very good source of information on "H.C.B." chemistry. A broader outlook results from the fact that the author has been practising chemistry for a long time in company with many worthy colleagues. However, the subject indicated by the title of the book is by no means exhaustively discussed. The book can be recommended to any critical reader. No library should be without this excerpt from the contemporary history of chemistry.

Roland Köster [NB 202 E]

Ullmanns Encyklopädie der technischen Chemie (Ullmann's Encyclopedia of Industrial Chemistry). Editorial board: *E. Bartholomé, E. Biekert, H. Hellmann*, and *H. Ley*. Edited by *H. Bucholz-Meisenheimer*.

Vol 1: General Principles of Process and Reaction Technology. Verlag Chemie, Weinheim. 4th Edit. 1972. xx, 644 pp., 328 figs., 132 tables, bound DM 315.—. Subscription price DM 285.—.

Vol. 2: Process Technology I (Unit Operations). 1972. xx, 764 pp., 949 figs., 92 tables, bound DM 315.—.

Vol. 3: Process Technology II and Reaction Equipment. 1973. xvi, 592 pp., 630 figs., 104 tables, bound DM 315.—.

Three of the planned six systematic volumes of the new edition of "Ullmann", publication of which was started in 1972, are now available; the first of the eighteen alphabetic volumes has meanwhile also appeared. Despite the change of publisher (the new edition is published by Verlag Chemie), the well-proven basic concept of the third edition has been kept unchanged[1]. The editorial board has wisely decided to revise the work completely instead of continuing it in the form of supplementary volumes. The latter possibility would have had the advantage of giving a more up-to-date result, but the unity and clarity offered by the new edition are probably more important to most of those who use the work, since true up-to-dateness can only be achieved by following the latest original publications.

The present three volumes, together with the fourth volume (Process Development and Plant Design), which has not yet been published, are descended from Volume 1 of the third edition. The enormous development that has taken place in chemical process technology during the past 20 years is clear simply from the greatly increased size of this systematic part. This is true in particular of the theoretical grounding and penetration of the field. For this reason the work as a whole begins with a special volume on scientific principles. This is followed by two volumes dealing with the unit operations of process technology together with the associated equipment, as well as general fields of process technology such as heating and cooling, materials, and pressure and vacuum technology.

The volume on basic principles (Vol. 1) consists of the following sections: Chemical Thermodynamics (53 pp.), Estimation of Physicochemical Properties of Gases and Liquids (28 pp.), Fluid Dynamics (35 pp.), Heat Conduction and Heat Transfer (13 pp.), Diffusion and Mass Transfer (28 pp.), Chemical Kinetics (36 pp.), Dimensional Analysis and Similitude (16 pp.), Principles of Chemical Reaction Engineering (75 pp.), Statistical Methods in the Planning and Evaluation of Experiments (68 pp.), Optimization (58 pp.), Mathematics (194 pp.).

The essential contents of the individual sections are definitions and explanations of the fundamental concepts and derivations of the fundamental relationships. Examples are given to illustrate theoretical methods arising from these discussions; special mention may be made of the mathematical determination of material values and the statistical planning and evaluation of experiments.

The bibliographies at the end of each contribution are designed primarily to enable the reader to obtain further and more advanced information from monographs on the subject. All the contributions (written by a total of ten authors, all but one of whom work at universities) are characterized by clear and impressive presentation; this gives the volume a well-rounded and unified character.

Whereas the first volume had no equivalent in the previous edition, the next two volumes really are a new edition of the previous first volume, *i.e.* a thorough revision.

Volume 2 contains the sections: Size Reduction and Classification (80 pp.), Mineral Dressing (62 pp.), Mechanical Separation Processes for Two-Phase Systems (105 pp.), Mixing (63 pp.), Size Enlargement (31 pp.), Heating and Cooling (143 pp.), Physicochemical Separation Processes (241 pp.).

Volume 3 follows with contributions on: Materials and Noise Prevention (82 pp.), Pressure and Vacuum Technology (47 pp.), Conveying (54 pp.), Refrigeration and Cryogenics (67 pp.), Electrolysis (51 pp.), Photoreactions (15 pp.), Reactors (222 pp.); the contribution on reactors is further divided into the sections: Homogeneous Gas and Liquid Phase Reactions (34 pp.), Liquid-Liquid and Gas-Liquid Reactions (40 pp.), Noncatalytic Reactions with Solids (70 pp.), Reactions on Solid Catalysts (54 pp.), Electrothermal Furnaces (24 pp.).

The contributions are all divided into several subsections, generally written by different authors. For example, the contribution on physico-chemical separation processes (Vol. 2) consists of the parts: Distillation and Rectification, Liquid-Liquid Extraction, Absorption, Adsorption, Diffusion Separation Methods, Evaporators, Sublimation, Crystallization, Fractional Crystallization from the Melt, Separation by Freezing, Drying, Extraction of Solids. The number of authors who have contributed to Volumes 2 and 3 (49 and 35 respectively) is accordingly much greater than for Volume 1; in the established Ullmann tradition, these are all acknowledged experts, mainly from industry.

The contributions describe the particular principles and the practical execution of the procedures for the sector in question. The construction and operation of the equipment are thoroughly explained with the aid of illustrations; methods for the calculation and design of equipment are also dealt with in exemplary fashion.

In view of the extensiveness of the subject matter and its division into individual topics, as occurs in Volumes 2 and 3, and indeed as is necessary for a thorough presentation, overlapping has been unavoidable. One should also bear in mind that the division of the material undoubtedly depended in part on the authors who were available. The reviewer nevertheless feels that a more rigorous subdivision would have been possible in particular in the sections on "Heating and Cooling" and "Reaction Equipment", in the interests of a more unified and better-balanced description of these fields. In the section on Reaction Equipment, for instance, roasting processes are certainly overstressed, above all when one considers that they occupy almost as much space as the contributions on heterogeneously catalyzed gas reactions in fixed beds and in fluidized beds together. Reactors for radiation-chemical reactions, apart from photoreactions, are not discussed; this omission should be corrected in the alphabetic part. This is also to be recommended for the key words "Storage", "Aseptic Production Techniques", "Tabletting": the first as a fundamental operation that is important for all types of chemical plants, and the last two as processes that are used *e.g.* in the packaging of pharmaceuticals.

However, these critical remarks are not intended in any way to belittle the outstanding achievement of the editors and authors. These three general volumes are indisputably the most comprehensive and most up-to-date work in existence on the field of chemical process technology as a whole; this is true even as far as foreign literature is concerned. It is worth mentioning that the new Ullmann also contains lists of contents and indexes in English. The presentation, illustrations, and print are of outstanding quality. Each contribution is followed by a clearly arranged list of references.

As in the previous edition, these general volumes will be of immense assistance to anyone who is concerned with process problems, both as a source of general information and as a source of advice on special problems. The latter case will particularly concern the practical engineer or chemist confronted with the question which process and which equipment are most suitable for a given purpose. This question of the choice of processes and equipment, which is not discussed in the same depth in all the contributions of Volumes 2 and 3, should be treated on a broader basis in Volume 4, which will be available shortly.

Ulfert Onken [NB 199 IE]

[1] Cf. Angew. Chem. internat. Edit. 9, 647 (1970).

MTP International Review of Science. Inorganic Chemistry: Series One. Edited by *H. J. Emeléus*. Volume 4: Organometallic Derivatives of the Main Group Elements. Edited by *B. J. Aylett*. Butterworths, London, and University Park Press, Baltimore, 1972. 1st ed., 424 pp., numerous figures, bound £ 10.—.

The series "Inorganic Chemistry" comprises a total of ten volumes and an index volume. The *first* series contains important progress reports on work published during the period from about 1967 to 1971. The second series, which is of roughly the same size, is scheduled for 1974; it will contain reviews of publications from the period 1971—1973. Further series will follow at roughly equal intervals.

Volume 4 of the first series is divided into nine chapters, which largely embrace the field of the organometallic chemistry of the main group elements. The material is divided as follows: Organoalkali Metal Compounds (author: *P. West*); Organoderivatives of Zinc, Cadmium, and Mercury *(K. C. Bass)*; Organoboron Compounds *(K. Niedenzu)*; Aluminum, Gallium, Indium, and Thallium *(J. B. Farmer* and *K. Wade)*; Silicon, Part 1 *(V. Chvalovsky)*; Silicon, Part 2 *(H. Bürger)*; Germanium *(E. J. Bulten)*; Tin and Lead *(A. J. Bloodworth)*; Organic Compounds of Arsenic, Antimony, and Bismuth *(J. P. Crow* and *W. R. Cullen)*.

In these nine chapters the authors report the most important developments in the various fields during the years 1969 and 1970. The reports are based on 2608 literature references. All earlier review articles and books dealing with the field in question are generally also cited in the various chapters. The result is a very useful literature compilation, which cannot always be complete, owing to the width of the individual fields. This Volume 4 unfortunately does not contain a chapter on organometallic compounds of the elements of the second main group. However, the editor *B. J. Aylett* assures us that a chapter on this topic will be included in the above-mentioned volume in the second series.

The work is not a pure list of highlights, nor does it have the character of a detailed review. It adopts a reasonable intermediate position, and it is pleasing to note that it contains few printing errors. The presentation of the work is very good, and it can be recommended to any organometallic chemist as a literature survey.

Jochen Ellermann [NB 201 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal.

Interpretation of Mass Spectra. By *F. W. McLafferty*. W. A. Benjamin, Reading 1973. 2nd revised and enlarged edition, xix, 278 pp., bound $ 15.00; stitched $ 7.50.

Englisch für Chemiker—English for Chemists. By *F. L. Boschke*, *B. M. Crook*, and *G. N. Tomby*. Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart 1973. viii, 93 pp., stitched DM 12.50.

Environmental Literature. A Bibliography. By *G. F. Bennett* and *J. C. Bennett*. Noyes Data Corporation, Park Ridge 1973. viii, 134 pp., bound $ 18.00.

Drilling Mud and Fluid Additives. By *J. McDermott*. Volume 20 of the series "Chemical Technology Reviews". Noyes Data Corporation, Park Ridge 1973. x, 305 pp., bound $ 36.00.

Photographic Emulsions. Recent Developments. By *R. W. James*. Volume 21 of the series "Chemical Technology Reviews". Noyes Data Corporation, Park Ridge, 1973. x, 303 pp., bound $ 36.00.

Furans. Synthesis and Applications. By *A. Williams*. Volume 18 of the series "Chemical Technology Reviews". Noyes Data Corporation, Park Ridge 1973. x, 301 pp., bound $ 36.00.

Contents: Furan and Substituted Furans; Tetrahydrofurans; Benzofurans and Dibenzofuran; Dihydrobenzofuran; Dihydrofurans, Furanones, and Griseofulvins.

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The Cyclobutadiene Problem

By Günther Maier[*]

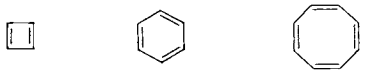
Dedicated to Professor Karl Winnacker on the occasion of his 70th birthday

Cyclobutadiene has recently become the center of reawakened interest. By use of the matrix isolation technique, cyclobutadienes can now be prepared as monomers frozen in matrices. Thus both the unsubstituted parent compound and its alkyl-substituted derivatives are amenable to study. The present progress report surveys the entire field; however, particular emphasis is placed on the author's own results from investigations concerning this classical problem of organic chemistry.

1. Introduction

About one hundred years have passed since *Kekulé*[1] turned his interest to the preparation of cyclobutadiene ("diacetylene") in his attempts to accomplish a total synthesis of a benzene derivative from aliphatic components. Like *Willstätter*[2], who attempted the first synthesis specifically directed towards cyclobutadiene around the turn of the century, *Kekulé* was unsuccessful.

These failures were unexpected; as vinylogs of benzene *(2)*, cyclobutadiene *(1)* and cyclooctatetraene *(3)* were ascribed "aromatic" properties, and therefore expected to exhibit pronounced stability.



(1) *(2)* *(3)*

The early pioneering studies simply could not lead to positive results because—as we now know—not only the experimental methods but also the theoretical concepts of the day prevented success. Nevertheless, *Willstätter* did actually synthesize cyclooctatetraene *(3)* by a laborious route[3]. The compound behaved in a completely unexpected manner. It had the character of a polyolefin and bore no resemblance whatsoever to benzene. However, all efforts to obtain cyclobutadiene in a similar fashion were in vain.

In view of these bitter disappointments it is understandable why about half a century elapsed until cyclobutadiene chemistry again came into its own during a second ten-year phase beginning in the mid-1950's.

All the attendant successes could not disguise the fact that in spite of enormous efforts—the papers published up to the end of 1965 fill a whole book[4]—nobody had been able to isolate the parent hydrocarbon or simply substituted derivatives, or even detect them as short-lived intermediates. This disappointing situation together with the discouraging pronouncements of theorists account for the delay of several years before a third assault was launched. The events of the most recent epoch provide the subject matter of the present report. It summarizes the author's own work in the field, supplemented by the most significant results from other workers' publications appearing during the past three years[5].

2. Theoretical Predictions

The contrasting behavior of cyclobutadiene and cyclooctatetraene on the one hand and benzene on the other long remained a mystery to the organic chemist. This was only to change

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355 Marburg, Lahnberge (Germany)

in about 1930 when *E. Hückel*[6] summarized the results of molecular orbital theory in the rule bearing his name. Accordingly, monocyclic conjugated polyenes having the general composition $(C_2H_2)_n$ ("annulenes") can be divided into two groups, *i.e.* into compounds containing $(4n+2)$ electrons and those with $(4n)$. Benzene is the simplest representative in the series of $(4n+2)$ systems which are stabilized by delocalization, while cyclobutadiene, necessarily being planar, is the prototype of the $(4n)$ class, which exhibits no particular stabilization in spite of the conjugated arrangement of double bonds.

The simple Hückel MO treatment predicts a zero π-delocalization energy for cyclobutadiene. The two nonbonding molecular orbitals are singly occupied; thus a triplet ground state is to be expected (Fig. 1). In contrast, VB theory indicates considerable resonance stabilization of the cyclobutadiene molecule. The gain in energy per electron is forecast to be even greater than that in benzene. A further result deriving from the VB method is that singlet cyclobutadiene may not possess a ground state of maximum symmetry (D_{4h}), but rather prefers an arrangement of lower symmetry (D_{2h}).

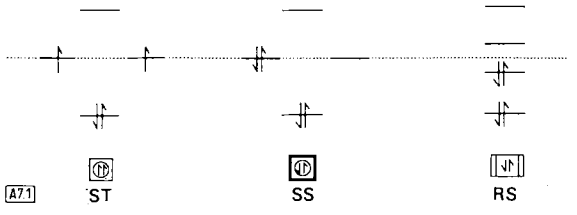


Fig. 1. MO schemes of cyclobutadiene. ST = square triplet, SS = square singlet, and RS = rectangular singlet molecule.

The above discrepancy reflects the difficulties inherent to the theoretical treatment of cyclobutadiene; in principle the two approximations should lead to the same result. Meanwhile[7], theoretical calculations have been refined and supplemented by new approximation methods[8-13]. Regardless of the method employed, the triplet ground state is found to be distinctly favored over a singlet variant for a square structure. The various methods also concur in predicting a square singlet molecule (SS) to be unstable owing to the Jahn-Teller theorem which requires a state of lower symmetry. By undergoing distortion the molecule attempts to achieve a more stable configuration; one possibility is a singlet cyclobutadiene having rectangular geometry (RS). Unlike the $(4n+2)$ annulenes in which bond alternance becomes significant only for a large number of ring members, such alternance is seen to be pronounced even for the parent compound of the $(4n)$ series, cyclobutadiene. However, the approximations are incapable of predicting exactly which of the two possibilities, square triplet (ST) or rectangular singlet cyclobutadiene (RS), should be the more stable. The energy difference between the ST and RS ground states will certainly be small. *Dewar*[12] has predicted a value of 2 kcal/mol (RS more stable than ST). Apart from rectangular distortions, others are also conceivable which likewise avoid the unfavorable SS configuration. The degeneracy of the middle π-MO's would also be resolved on deformation to a rhombus, a trapezium, or a folded structure (Fig. 2). (X-ray studies[14] on a "push-pull" cyclobutadiene of type *(4)* indicate that a rhomboid geometry represents a real possibility.)



Fig. 2. Alternative distortions in cyclobutadiene.

According to modern views, the energy content of cyclobutadiene is greater than that of the corresponding open-chain conjugated diene. Hence cyclobutadiene is characterized by a "negative resonance energy". It possesses antiaromatic character; the molecule is not stabilized by cyclic conjugation but destabilized instead[15-18]. In fact, the calculations would indicate cyclobutadiene to be an antiaromatic *par excellence*. An increase in energy content of 18 kcal/mol—and even about 34 kcal/mol for the SS configuration—has been predicted by *Dewar*[12]. The same method yields a decrease of 20 kcal/mol in the energy content of benzene. In each case, the reference level is the enthalpy of formation of the corresponding classical polyene which can be determined with considerable accuracy. Calculated and measured values are in agreement for the aromatic benzene (adoption of the conjugated polyene as energy reference leads to the value of 20 instead of the usual 36 kcal/mol); experimental proof has yet to be obtained for the antiaromatic cyclobutadiene (Fig. 3).

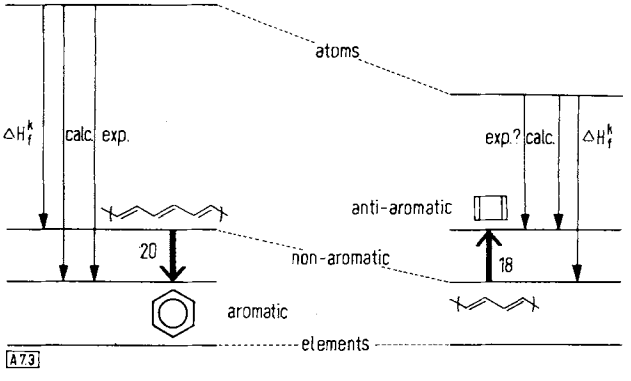


Fig. 3. Distinction between an aromatic and an antiaromatic compound, schematic. Energies are given in kcal/mol.

Benzene and cyclobutadiene are worlds apart. The former possesses an ideally delocalized π-electron system. The two Kekulé structures *(2a)* and *(2b)* (Fig. 4) are fictitious resonance structures serving merely to describe the resonance-stabilized molecule. The delocalization energy (DE) is considerable. Completely different conditions are found in cyclobutadiene. Assuming a rectangular singlet ground state, then the two structures *(1a)* and *(1b)* describe two valence isomers, *i.e.* real species in mutual equilibrium: they are separated from each other by an energy barrier (E_A)[19]. The square structure having equal bond lengths describes the transition state of valence isomerization between two forms having

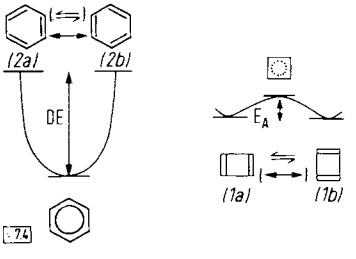
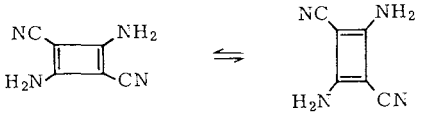


Fig. 4. Distinction between resonance (mesomerism) and valence isomerism (examples: benzene and cyclobutadiene, respectively).

alternating bond lengths (Fig. 4). It is extremely difficult to predict[12] the height of the energy threshold. On the one hand, the geometrical prerequisites for bond transfer are optimally fulfilled and the process could proceed very rapidly; on the other hand, if it is permissible to equate the transition state with SS cyclobutadiene, then an activation barrier of at least $34-18=16$ kcal/mol is to be expected. An essential requirement is that the transition *(1a)*⇌*(1b)* should not be bound up with a change in multiplicity to triplet cyclobutadiene. In other words: it is unclear to what extent the principle of conservation of orbital symmetry will oppose this fluctuation.

A value of about 3 kcal/mol was calculated in the case of the donor-acceptor substituted cyclobutadiene *(4)*[20].



(4a) *(4b)*

3. Statement of Problem

This brief summary shows that the cyclobutadiene problem not only possesses great theoretical interest but also represents a challenge to the experimental organic chemist. Anybody seeking a solution will have to answer the following questions:

1) Are synthetic methods available which permit the generation of cyclobutadienes at very low temperatures?

2) Is it possible to create conditions under which these cyclobutadienes can exist as monomers?

3) What is the multiplicity of cyclobutadienes in the ground state? Is there any relation between multiplicity and substitution pattern?

4) What geometry do cyclobutadienes possess in the ground state? Does this geometry vary depending on the presence of singlet or triplet molecules?

5) Do cyclobutadienes display characteristic spectroscopic properties? Do the spectra provide any information about the electronic situation, and do they permit assignment to a particular electronic configuration?

6) Are there any chemical reactions typical of cyclobutadienes? Can any characteristic differences be observed between singlet and triplet cyclobutadienes?

7) Can an equilibrium be detected between two valence isomeric forms of suitably substituted derivatives? How high is the energy barrier for this process?

8) What is known about the valence-isomeric relationship cyclobutadiene/tetrahedrane?

9) Is cyclobutadiene really the prototype of an antiaromatic compound, as required by theory? How great is the destabilization?

Even if a suitable synthetic route were to be found and the existence of monomer proved, further important points still remain to be established: The multiplicity still has to be elucidated by ESR studies and the geometry by X-ray studies or analysis of IR and Raman spectra. UV and photoelectron spectra will have to be consulted to obtain valid information about the electronic situation in the cyclobutadiene molecule. NMR spectra will be required for observation of a possible coalescence phenomenon and the expected paramagnetic ring current. And finally, experimental determination of the heat of combustion or hydrogenation must be performed in order to establish the energy content.

If anything, the earlier experimental observations made one fact very clear: the lifetime of cyclobutadiene—with the exception of cyclobutadienes modified by fusing with aromatic systems[21] or by a "push and pull" effect[22], and of course cyclobutadiene complexes[23], *e.g. (81)*—is certainly so short that isolation appears hopeless. Studies by flash pyrolysis[24–26] and flash photolysis[27–29] had shown the lifetime of the unsubstituted parent to be probably no more than a few ms. If an attempt to isolate cyclobutadienes is not to be condemned to failure from the outset, then conventional thermal preparations are immediately ruled out. Instead, a method must be chosen which permits generation of cyclobutadienes at extremely low temperatures. Hence only a photochemical process comes into question.

We have devoted our efforts to the synthesis of photoprecursors suitable for generating cyclobutadienes in order to fulfill the long-standing wish for a direct spectroscopic observation of cyclobutadiene and its derivatives by means of the matrix isolation technique.

4. Method

In the matrix isolation technique[30, 31] highly reactive species are frozen in a matrix at extremely low temperatures. Organic solvent glasses are employed as matrices in which the species resulting on photofragmentation are capable of existence as monomers owing to the extremely low rate of diffusion, and are thus amenable to direct observation. Hydrocarbons, perfluorinated organic compounds, ethers, and alcohols (particularly multicomponent systems in various mixing ratios) are suitable for use as UV-transparent inert solvents. Liquid nitrogen (77 K) can be used for quenching. After irradiation and melting of the matrix the products are isolated and identified in the usual way. Recently, noble gases, especially argon, have found increased application as guest matrices. The necessary cells and cooling systems—liquid helium (4 K) in open or closed circulation—have recently become commercially available.

5. Methylated Cyclobutadienes

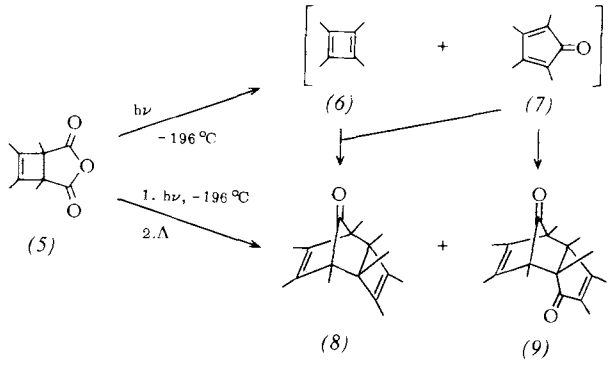
Suitable precursors for photochemical generation of cyclobutadienes are cyclobutenedicarboxylic anhydrides which can be prepared by sensitized photoaddition of correspondingly substituted acetylenes to maleic anhydrides.

Surprisingly, these anhydrides exhibit pronounced maxima between 228 nm (unsubstituted anhydride) and 241 nm (tetramethylated derivative) owing to homoconjugative interaction of the C=O group with the C=C double bond. The position of the maximum shifts towards longer wavelengths with increasing number of alkyl groups.

Irradiation of tetramethylcyclobutenedicarboxylic anhydride *(5)*[32] affords a complicated mixture of products[33]. The crucial intermediates for formation of the twelve isolated and identified products are the monoketone *(8)* and the diketone

(9). Formation of these two compounds can be regarded as evidencing the intermediacy of tetramethylcyclobutadiene (6) and tetramethylcyclopentadienone (7).

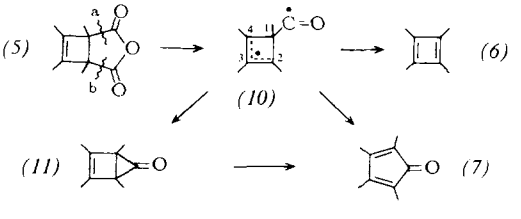
Support for this view comes from the results of low temperature photolysis[34] of (5). On irradiation in a matrix (ethanol/ether/isopentane) at −196 °C a deep yellow coloration is observed which vanishes immediately upon thawing, even before the



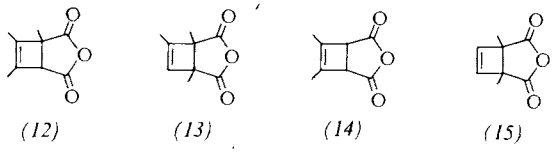
glass has completely melted. Only the two adducts (8) and (9) can then be isolated as products. On irradiation in a matrix under the same conditions these adducts give the same product mixture as is found on irradiation of (5) in solution at room temperature. Thus it is clear that on irradiation of (5) no adduct (8) or dimer (9) is present prior to thawing of the matrix and that tetramethylcyclobutadiene (6) and cyclopentadienone (7) must be frozen in the matrix as monomers. Provided that the matrix is kept at −196 °C, the yellow color is retained for several hours after the lamp has been switched off. It may be assumed that the stability of (6) and (7) under these conditions is due less to the low temperature than to the greatly reduced mobility of the molecules in the frozen state.

In order to gain an insight into the mechanism of the fragmentation reaction we have also subjected partially methylated anhydrides to photocleavage. The distribution of the methyl groups in the products can provide an indication of whether cyclobutadienes really do occur as intermediates, for other reactions are conceivable which could also explain the formation of key substances like (8) or (9).

All available evidence suggests that the primary step in photocleavage of, *e. g.* the anhydride (5), is liberation of CO_2. The diradical fragment (10) can then react by one of two possible routes. It can either undergo CO elimination to form the cyclobutadiene (6) or recombination at position 2 or 4 to give a cyclopentadienone. We cannot yet say whether this isomerization proceeds directly or *via* a bicyclopentenone intermediate (11). A number of findings—it is impossible *e. g.* to detect compounds of type (11) in a matrix by IR spectroscopy—appear to favor the one-step reaction of (10) giving (7).

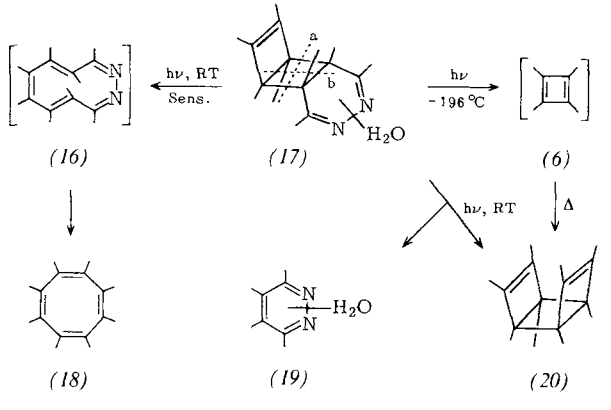


This is supported by studies in the series of anhydrides (12)[32], (13)[35], (14)[32], and (15)[35], and especially by the substitution pattern in the products of room temperature photolysis of (12)[36] and (14)[37]. (When the substituents are different, cf. formula (5), rupture of bonds a and b leads to two different diradicals.) Quantitative determination of the total of 19 known structurally elucidated products resulting on cleavage of the anhydride (14) also permits one to conclude that steric factors exert a certain selectivity in 1,2-dimethylcyclobutadiene[37]. The doubly substituted double bond is less reactive than the unsubstituted one.



Low temperature photolysis[34, 36] of the partially methylated anhydrides (12)—(15) also displays the expected picture. Both (12) and (14) give a yellow matrix on cleavage at −196 °C. Again, after melting of the glass, only adducts of cyclobutadienes to cyclopentadienones and dimers of the corresponding cyclopentadienones, but no secondary photoproducts of these compounds, are found. In contrast, photofragmentation of monomethylated cyclobutenedicarboxylic anhydrides takes an exceptional course[35].

The yellow color observed on cleavage of tetramethylcyclobutenedicarboxylic anhydride (5) at −196 C can be due to both cyclobutadiene (6) and cyclopentadienone (7). Proof that the cyclobutadiene system is capable of existence as the monomer under the conditions applied, and is possibly characterized by a typical UV absorption, is feasible only if an independent synthetic pathway for photochemical generation of cyclobutadiene (6) is available. Formation of cyclopentadienone must be ruled out completely.



As an example of such a method we can consider the photofragmentation of the heterocycle (17). Irradiation of (17)[38] gives an almost quantitative yield of the *syn*-tricycle (20) and tetramethylpyridazine (19). In this context it may be mentioned that octamethylcyclooctatetraene (18) is formed almost exclusively on sensitization with benzophenone[39]. Apparently (17) is cleaved across a on direct irradiation, while ring-opening across b to yield a diaza[10]annulene (16) is preferred on sensitization. The latter product then furnishes the hydrocarbon (18) by elimination of nitrogen. The change

in stereochemistry on going from the *anti*-configurated heterocycle *(17)* to the *syn*-tricycle *(20)* proves the intermediacy of cyclobutadiene *(6)* in the unsensitized irradiation.

It is especially interesting that on irradiation of *(17)* in a matrix at −196 °C a yellow coloration is again observed which is stable only under these severe conditions and disappears on removal of the liquid nitrogen. As products, the hydrocarbon *(20)* and tetramethylpyridazine *(19)* can be detected in more than 90% yield. Since *(19)* absorbs at 258.5 nm it should now be possible to detect tetramethylcyclobutadiene *(6)* directly by UV spectroscopy. Whereas a broad maximum at 423 nm is found on photochemical cleavage of the anhydride *(5)* in a low-temperature cell, a maximum at 375 nm appears in the case of *(17)* when exposed to identical conditions (Fig. 5). This absorption must be asssigned to tetramethylcyclobutadiene *(6)*.

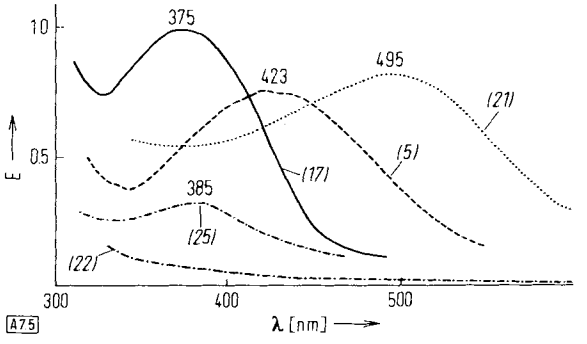
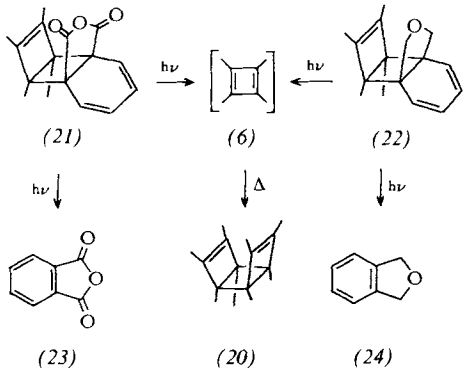
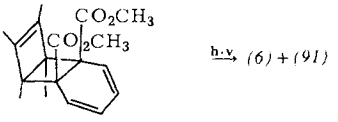


Fig. 5. Low-temperature UV spectra starting from *(5)*, *(17)*, *(21)*, *(22)*, and *(25)*; layer thickness 1 mm. The spectra correspond to tetramethylcyclopentadienone *(7)*, the charge-transfer complexes *(26)*, *(27)*, and *(28)*, and free tetramethylcyclobutadiene *(6)* (see text).

The only possible source of error could arise from the maximum at 375 nm being due not to the "free" cyclobutadiene but to a charge transfer complex between *(6)* and the pyridazine *(19)*. In order to reach a decision in this matter, we have searched for other photoprecursors for an independent generation of *(6)*. The principle employed in cleavage of *(17)*, namely that of forcing formation of *(6)* by elimination of a component stabilized by delocalization, should also be applicable to compounds *(21)* and *(22)*. Indeed, both substances smoothly form the tricycle *(20)* on room-temperature irradiation. Compound *(21)*[40] yields phthalic anhydride as second product; *(22)* eliminates phthalan *(24)*, and *(25)* dimethyl phthalate *(91)*[41]. The same applies to low-temperature photolysis. If the fragmentation is performed in a low-temperature cell at −196 °C, then in the case of *(21)* a deep red coloration is observed which is due to a maximum at 495 nm. On cleavage of *(22)* neither a coloration nor a maximum above 300 nm is observed (Fig. 5). If a very thin layer (0.1 mm) is irradiated, then, in addition to the spectrum of the cleavage product *(24)*, an absorption can be seen which gradually increases from 300 nm towards shorter wavelengths.



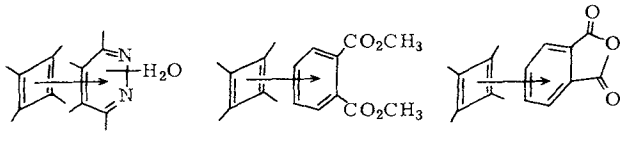
We are now in a position to produce tetramethylcyclobutadiene *(6)* by five independent routes[42], starting from *(5)*, *(17)*, *(21)*, *(22)*, or *(25)*. However, a different UV spectrum is recorded for each one of these fragmentations. How can



(25)

these contradictory results be explained? Presumably tetramethylcyclobutadiene is an excellent electron donor. Should cleavage of *(17)* or *(21)* simultaneously generate an acceptor molecule, a charge-transfer complex can be formed in the matrix. The necessary geometrical arrangement is already provided by the starting materials. This possibility does not exist in the case of the anhydride *(5)* where the donor and acceptor (cyclopentadienone) arise from different starting molecules.

These considerations permit the following assignments: the maximum at 423 nm observed on cleavage of *(5)* is due solely to tetramethylcyclopentadienone *(7)*. The 375-nm band seen in the case of *(17)* comes from the charge-transfer complex *(26)*. The absorption at 385 nm resulting on cleavage of the ester *(25)* indicates the presence of complex *(27)*. Even more pronounced is the interaction in complex *(28)*: hence the band at 495 nm when *(21)* is used as precursor. Only the fragmentation of *(22)* generates free tetramethylcyclobutadiene *(6)* (phthalan does not possess acceptor properties).



(26) *(27)* *(28)*

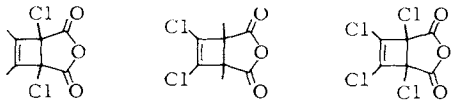
However, the absorption of *(6)* apparently lies below 300 nm, in accord with the theoretical predictions[9] for rectangular singlet cyclobutadiene which should display no further allowed transitions above 197.7 nm ($f = 0.21$).

6. Chlorinated Cyclobutadienes

According to studies by *Cava*[43], halogen atoms can exert a significant stabilizing effect on the naphthocyclobutadiene system. Presumably the halogen atoms have a dual action: by way of their inductive effect (reduction of the charge density in the ring) and their mesomeric effect ("push-pull" interaction between the substituents and the π-system of cyclobutadiene).

Nothing is yet known about the degree of stabilization in simply substituted cyclobutadienes[44-47]. We have therefore irradiated the chlorinated anhydrides *(29)*[48], *(30)*[49], and

(31), hoping to detect these species directly in the matrix by spectroscopy and to glean some information about the extent of stabilization by the chlorine atoms from the behavior of the system on thawing. The experiments[50] not only con-

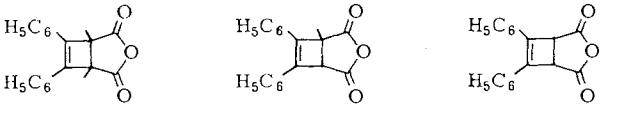


(29) *(30)* *(31)*

firmed the fragmentation mechanism discussed in Section 5 [*(29)* and *(30)* both afford the same adduct of 1,2-dichloro-3,4-dimethylcyclobutadiene to 2,3-dichloro-4,5-dimethylcyclopentadienone as required] but also show that the chlorine atoms at least prolong the lifetime of the cyclopentadienone ring system. However, no unequivocal statement can be made whether the same applies to the cyclobutadiene ring system.

7. Phenylated Cyclobutadienes

By virtue of their mesomeric effect, phenyl groups should have an even more favorable influence on the cyclobutadiene ring system than chlorine atoms. As a supplement to the investigations by *Freedman*[51] and *Pettit*[52], it seemed reasonable to generate phenylated cyclobutadienes in a matrix at −196 °C by photofragmentation of the anhydrides *(32)*, *(33)*, and *(34)*, and to study the degree of interaction with the



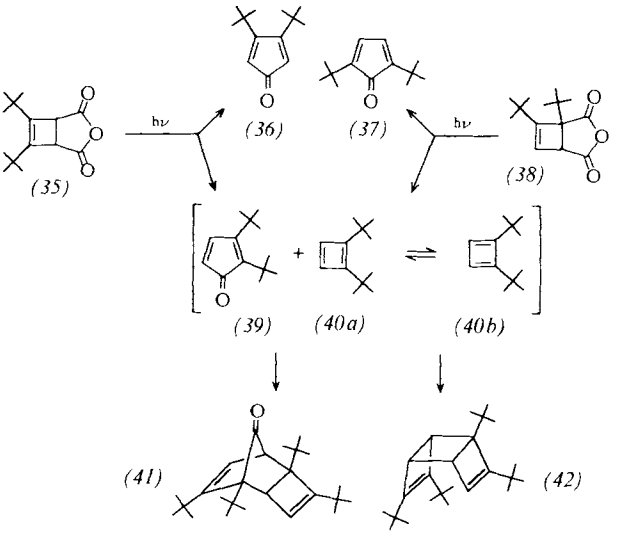
(32) *(33)* *(34)*

phenyl groups. The anhydrides are readily accessible by photoaddition to tolan[53], but unfortunately turn out to be too photostable. By promoting distribution of the absorbed energy, the phenyl groups preclude photocleavage. Even several hours' irradiation leads to minimal conversions.

8. *tert*-Butylated Cyclobutadienes

The predicted antiaromaticity of cyclobutadiene would lead one to expect a high reactivity, particularly with regard to a Diels-Alder-like dimerization. Introduction of *tert*-butyl groups represents a method of preparing sterically hindered but electronically intact cyclobutadienes[54–58]. We have attempted to apply the photofragmentation reaction to *tert*-butylated anhydrides with the aim of preparing not only stable cyclopentadienones, but possibly even isolable cyclobutadienes.

Low temperature photolysis of 3,4-di-*tert*-butylcyclobutenedicarboxylic anhydride *(35)*[59] affords 3,4-di-*tert*-butylcyclopentadienone *(36)*, which can exist as the monomer, as well as two additional products, the monoketone *(41)* and hydrocarbon *(42)*. Owing to steric hindrance in the transition state, the dienone *(36)* fails to dimerize even at room temperature. It does not even add 1,2-di-*tert*-butylcyclobutadiene *(40)*. The latter is only able to form the adduct *(41)* with the



(35) *(36)* *(37)* *(38)* *(39)* *(40a)* *(40b)* *(41)* *(42)*

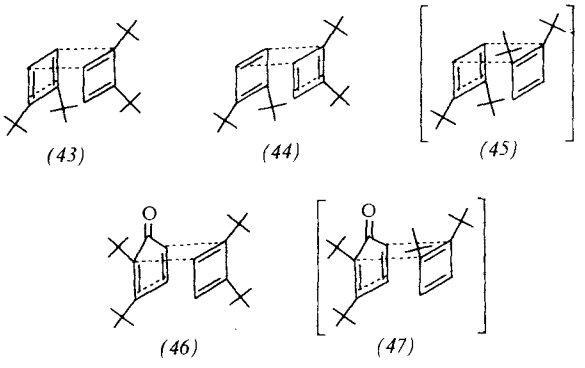
2,3-di-*tert*-butylcyclopentadienone *(39)* likewise present in the matrix. The unconsumed cyclobutadiene dimerizes to the tricycle *(42)*[36].

If the positional isomer *(38)* is irradiated under analogous conditions, compounds *(41)* and *(42)* are again obtained after thawing of the matrix. Instead of the dienone *(36)*, the monomeric 2,5-di-*tert*-butylcyclopentadienone *(37)* can then be isolated.

These findings[60] constitute additional proof of the cleavage scheme proposed above. Moreover, it is apparent that two *ortho tert*-butyl groups can stabilize the cyclopentadienone, but not the cyclobutadiene, ring system to such a degree as to render it isolable.

Of greater importance is the fact that the above results can be regarded as evidence for a valence-isomeric equilibrium *(40a)*⇌*(40b)*. The distribution of substituents in *(42)* reveals that either two 1,4-isomers *(40b)* must have reacted according to formula *(43)* or two 1,2-isomers *(40a)* according to *(44)*. Although apparently more likely from statistical considerations, combination *(45)* does not seem to come into play. The substitution pattern in adduct *(41)* results from addition of the 1,4-valence isomer *(40b)* to the dienone *(39)* [transition state *(46)*]. Diels-Alder reaction of *(40a)* [transition state *(47)*] would lead to a different product.

The simplest explanation is the following: the same valence-isomeric system *(40a)*⇌*(40b)* is formed from both *(35)*

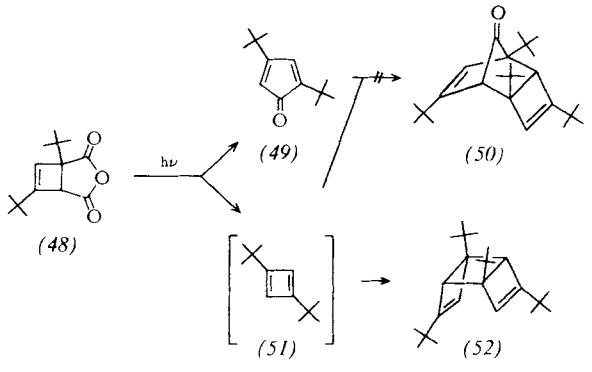


(43) *(44)* *(45)* *(46)* *(47)*

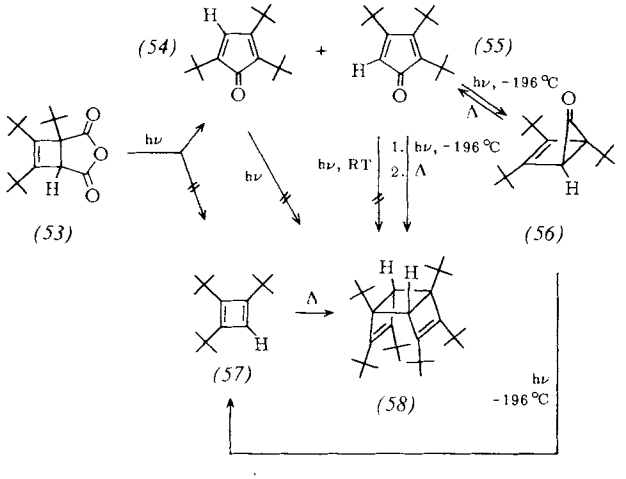
and *(36)*; however, the equilibrium lies completely on the side of the 1,4-isomer *(40b)* in which the bulky substituents

are farthest apart. A similar situation is discussed by *Pettit*[52] for "*ortho*"-(1,2- and 1,4-)diphenylcyclobutadiene.

Owing to its greater inherent steric hindrance 1,3-di-*tert*-butylcyclobutadiene *(51)* should be less prone to undergo Diels-Alder reaction than *(40)*. This prediction is confirmed by experiment[60]. Irradiation of the anhydride *(48)*[61] gives only two products, *i.e.* 2,4-di-*tert*-butylcyclopentadienone *(49)* and the dimer *(52)* of 1,3-di-*tert*-butylcyclobutadiene *(51)*. Enclosed in the matrix, *(51)* can no longer undergo Diels-Alder reaction with the dienone *(49)* to give *(50)*. Nevertheless, it is still sufficiently reactive to give *(52)* by self-addition.



The ideal starting material for preparation of tri-*tert*-butylcyclobutadiene, which, according to the above arguments, might be stable enough to be detectable as the monomer in solution, would appear to be the anhydride *(53)*. However, its photocleavage leads exclusively to the two cyclopentadienones *(54)* and *(55)*. Neither cyclobutadiene *(57)* nor its dimer *(58)* is found.



We explain this disappointing reaction course as being due to preferential formation of the former of the two conceivable diradical intermediates *(59)* and *(60)* because in this form the third *tert*-butyl group possesses a staggered orientation. Elimination of CO from *(59)* would necessarily lead to an eclipsed arrangement of all *tert*-butyl groups and is therefore precluded.



Thus the problem arises of finding an alternative path for the synthesis of tri-*tert*-butylcyclobutadiene *(57)*. One possibility that springs to mind is the anodic oxidation of the dianion of the dicarboxylic acid parent of anhydride *(59)*[62]. Performed under the usual conditions, Kolbe electrolysis affords only 1,2-di-*tert*-butyl-3-pivaloylcyclopropene[63] and the diketone *(66)*[63] as defined isolable products; under very mild conditions a low yield of 2,3,5-tri-*tert*-butylfuran[64] is obtained. These results suggest that anodic oxidation of 1,3,4-tri-*tert*-butylcyclobutenedicarboxylic acid does indeed lead to tri-*tert*-butylcyclobutadiene *(57)*, but the sensitivity of this species towards oxygen represents a serious obstacle to its detection.

In spite of all these difficulties we refused to capitulate, and our perseverance was finally rewarded[65]: If the photofragmentation of *(53)* at −196 C is followed by IR spectroscopy, the carbonyl band due to the cyclopentadienones *(54)* and *(55)* is seen to exhibit a partial drop in extinction on prolonged irradiation. A detailed study showed that *(54)* is photostable at all temperatures. The same applies to *(55)* at room temperature. Strangely enough, however, *(55)* undergoes photocleavage at −196 °C. Low-temperature IR spectra betray the formation of CO. Under favorable conditions, the tricyclic hydrocarbon *(58)* is isolated in over 80% yield on thawing of the matrix.

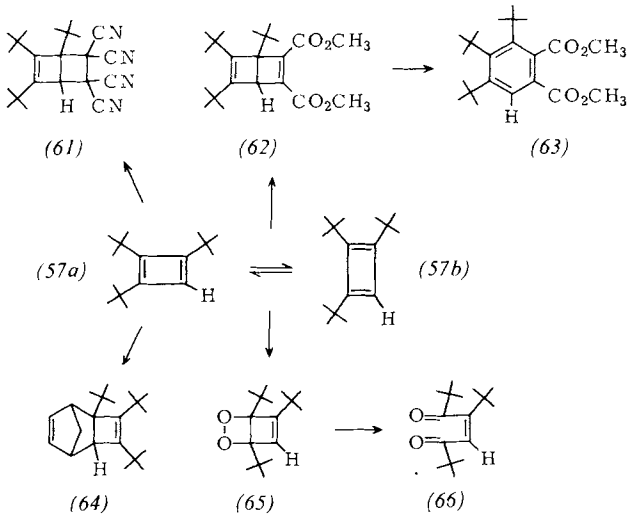
We explain this surprising result in the following way: The three adjacent *tert*-butyl groups in *(55)* induce the molecule to transform into the bicyclic compound *(56)*. The thermal reverse reaction is so fast at room temperature that the steady-state concentration of *(56)* is extremely low. At −196 C, however, the concentration is sufficiently high (although still not high enough for detection by IR spectroscopy) to play a product-forming role in the reaction. Elimination of CO leads to the long-sought tri-*tert*-butylcyclobutadiene *(57)*.

On irradiation for three hours at −196 C in a perdeuterated methylcyclohexane glass (sealed NMR sample tube), *(55)* is converted almost completely into a new species which survives thawing to room temperature and is characterized by three signals in the 100-MHz ^{1}H-NMR spectrum [τ=4.65 (1H), 8.86 (9H), and 8.95 (18H)]. After 24h only the spectrum of the dimer *(58)* can be recorded. Thus there can be no doubt that the intermediate is tri-*tert*-butylcyclobutadiene *(57)*.

We not only accomplished the first preparation of a cyclobutadiene stable at room temperature which bears only alkyl substituents and must consequently have an intact π-electron system, but were also able to determine the chemical shift of a proton attached directly to the cyclobutadiene ring and thus to obtain an indication of the paramagnetic ring current in cyclobutadiene.

The equivalence of the two *tert*-butyl groups of *(57)* which are adjacent to the proton in question can be viewed as an argument favoring a fast valence isomerization *(57a)*$\rightleftharpoons$*(57b)*, provided that *(57)* possesses a singlet ground state with alternating bond lengths.

The successful preparation of *(57)* now permits unique characterization of the typical reactions of a cyclobutadiene[66]. In this context, the readiness to undergo Diels-Alder reactions and the ease of autoxidation warrant particular attention. Tri-*tert*-butylcyclobutadiene *(57)* readily forms adducts not only with maleic anhydride[67], but also with tetracyanoethylene and dimethylacetylenedicarboxylate, attack taking place



(61) (62) (63)

(57a) (57b)

(64) (65) (66)

exclusively at the less substituted double bond. It is characteristic for the adduct *(61)* that the bridgehead *tert*-butyl group gives a separate NMR signal for each methyl group owing to hindered rotation, provided that acetone is used as solvent; no splitting is observed in benzene. The Dewar-benzene derivative *(62)* is stable at 100 °C but isomerizes to dimethyl 3,4,5-tri-*tert*-butylphthalate *(63)* at 150 °C. Compound *(63)* can also be obtained by diene synthesis with the cyclopentadienone *(55)*[68].

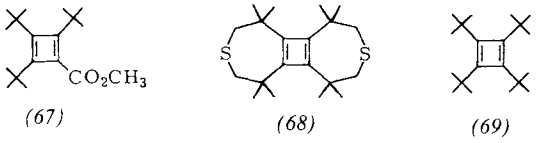
In the examples cited so far, *(57)* reacts as a diene. Its ability to function as a dienophile is manifested in its reaction with cyclopentadiene. The NMR spectrum[69] of the product indicates structure *(64)*.

It is therefore hardly surprising that the dimerization of *(57)*, which is also classified as a Diels-Alder reaction, is relatively fast in spite of pronounced steric hindrance. The activation enthalpy and activation entropy of this reaction may be expected to have highly unusual values. Kinetic studies are in progress[66].

Particular interest attends the reaction of the cyclobutadiene *(57)* with oxygen, on the one hand because a compound is formed to which we are forced to assign the structure of a cyclobutene ring fused to a dioxetane. The NMR and IR spectra, the positive reaction with potassium iodide solution, and the ready conversion into the unsaturated diketone *(66)* constitute structural proof of *(65)*. This latter isomerization occurs even at room temperature. On the other hand, autoxidation occupies a special place in that it occurs specifically at the doubly substituted double bond. The reason could lie in the stepwise nature of the reaction, in contrast to the course of the Diels-Alder reactions.

It is of course very tempting to apply the above method to the synthesis of tetra-*tert*-butylcyclobutadiene *(69)*. Preparation of the starting materials presents a serious obstacle, however. Meanwhile, this gap has largely been closed by the work of *Masamune*[67] and *Krebs*[70]. *Masamune* has not only generated tri-*tert*-butylcyclobutadiene *(57)* and detected it in solution, almost simultaneously with and independently of us, but also isolated the ester *(67)*; the method of choice was also low-temperature irradiation of suitable photoprecursors (cyclopropenyldiazomethane derivatives).

Thermal dimerization of strained cycloalkynes represents another entry to these compounds. Experiments with unsubstituted[71] and tetramethylated cyclohexyne[72] remained unsuccessful; however, by using the corresponding $PdCl_2$ complex *Krebs* has been able to prepare the cyclobutadiene derivative *(68)*, the first example of a cyclobutadiene stabilized by steric

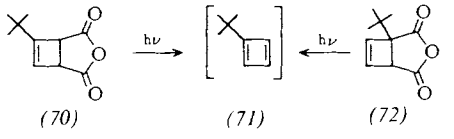


(67) (68) (69)

hindrance. On exclusion of oxygen the crystalline product is completely stable at room temperature. The question as to the extent of possible stabilization by the sulfur atoms has been answered by the photoelectron spectrum[73]: no transannular n/π interaction exists.

9. Unsubstituted Cyclobutadiene

It was our aim to arrive at stable cyclobutadienes by introducing bulky residues. In addition, we had also set ourselves the task of establishing the existence of unsubstituted cyclobutadiene *(1)* with the aid of the matrix method. The photofragmentation of the mono-*tert*-butyl-substituted anhydrides *(70)*[74] and *(72)* leads up to the second kind of problem. Both anhydrides should yield the same cyclobutadiene *(71)*, *i.e.* starting from *(70)* and *(72)* the same UV spectrum should



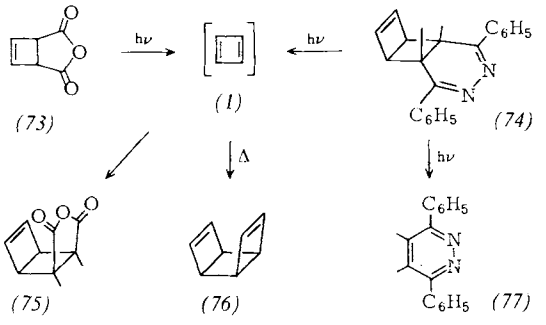
(70) (71) (72)

be obtained on low temperature photolysis. This is indeed the case[75] (Fig. 6). During matrix irradiation, a maximum appears between 300 and 305 nm which is presumably due to *tert*-butylcyclobutadiene *(71)*. The assignment is relatively easy since IR analyses have established that only little cyclopentadienone results on photofragmentation of *(70)*, and none at all is formed from the positional isomer *(72)*. It should be emphasized that the absorption maximum recorded here is completely different from that obtained in the case of tetramethylcyclobutadiene (Fig. 5).

What is the situation regarding unsubstituted cyclobutadiene itself? Publications by *Nenitzescu*[76] and *Pettit*[77] convincingly demonstrate that cyclobutadiene *(1)* has to be assumed as an intermediate in the dehalogenation of 3,4-dichlorocyclobutene and oxidative decomposition of the $Fe(CO)_3$ complex *(81)*.

A fitting climax to our experiments would be the generation of the parent compound *(1)* in a matrix starting from the anhydride *(73)*[78,79]. The relatively short-wave absorption maximum of *(73)* at 228 nm with an extinction of only 670 represents an experimental problem. Thus it is difficult to excite the molecule with 253.7 nm light. Irradiation of *(73)* at room temperature in methylene chloride results only in dimerization[80]. If this intermolecular reaction is suppressed by embedding the anhydride in a matrix (ether/tetrahydrofur-

an/isopentane) it is indeed cleaved as desired on irradiation[75], albeit to a limited extent. The IR spectra indicate formation of CO_2 and CO. After eight hours' irradiation a 9% yield of the *syn*-tricyclic compound *(76)* is isolated as sole product on thawing of the matrix[75,80]. Of greater significance is



the reoccurrence of a maximum at 301 nm in the UV spectroscopic record of the fragmentation of *(73)* (Fig. 6). This band vanishes immediately on warming. The position of the maximum corresponds to that observed on irradiation of the anhydrides *(70)* and *(72)*. There is a conspicuous difference between these spectra and those of tetramethylcyclobutadiene reproduced in Figure 5.

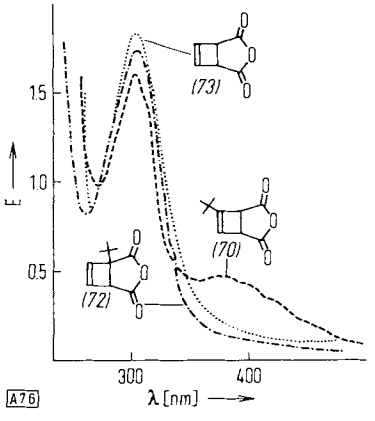
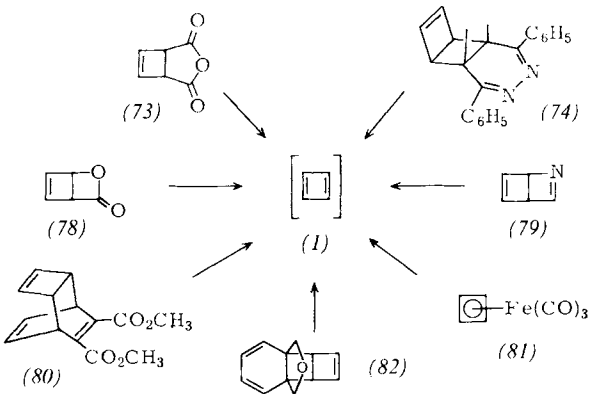


Fig. 6. Low-temperature UV spectra starting from *(70)*, *(72)*, and *(73)*; layer thickness 1 mm. The first two spectra correspond to *tert*-butylcyclobutadiene *(71)*, and the other to cyclobutadiene *(1)*.

Assignment of the band at 301 nm to unsubstituted cyclobutadiene *(1)* would stand on a firmer footing if the same absorption were to be observed on fragmentation of another photoprecursor. For this reason, we synthesized the heterocycle *(74)*, by analogy with *(17)*, and irradiated it under the same conditions at −196 °C. Although fragmentation to cyclobutadiene and 4,5-dimethyl-3,6-diphenylpyridazine *(77)* does in fact occur, as desired, the conversion is so low (owing to the phenyl groups, cf. Section 7) that the UV maximum of *(1)* cannot be differentiated against the strong absorption of the pyridazine. On heating, the tricyclic compound *(76)* is again formed as sole product from *(1)*. It is not found on room-temperature irradiation of *(74)*. If irradiation is performed in the presence of an excess of dimethylmaleic anhydride, then a small amount of adduct *(75)* can be detected. A crucial breakthrough, at least as far as unsubstituted cyclobutadiene is concerned, was accomplished by two American research groups: both applied the matrix isolation technique to photolysis of the lactone *(78)*. *Corey*[81] first synthesized this compound ten years ago, and remarked at the time that



it should be an ideal precursor for generation of cyclobutadiene. This prediction is confirmed by the observation that irradiation of *(78)* in presence of carbonylmetal compounds yields cyclobutadiene complexes[82]. The photochemical behavior of α-pyrone and its bicyclic isomer *(78)* accordingly remained a center of avid interest[83–85]. Nevertheless, success did not follow immediately. Only very recently, *Chapman*[86] and *Krantz*[87] independently generated cyclobutadiene *(1)* by irradiation of *(78)* in noble gas matrices at temperatures of 8—20 K and characterized it by means of its IR spectrum. Analogous investigations with deuterated[13,88] derivatives of *(78)* leave no doubt that the IR spectrum recorded really is due to cyclobutadiene *(1)*[**].

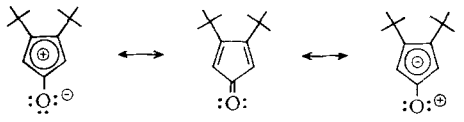
Furthermore, *Masamune*[89] observed a UV maximum at 300—305 nm when he subjected the cyclic ether *(82)* to photocleavage in a matrix at −175 °C. This constitutes independent confirmation of our spectral observations. It may thus be assumed that this absorption behavior is peculiar to cyclobutadiene *(1)*. While such a band contradicts theoretical predictions regarding the electronic spectrum of singlet cyclobutadiene, a certain agreement is found with the calculated[9] absorption ($\lambda_{max} = 380$ nm; $f = 0.2$) for square triplet cyclobutadiene.

Meanwhile, a whole series of precursors has become available for the generation of cyclobutadiene. To the compounds *(73)*, *(74)*, *(78)*, and *(82)* already mentioned, we can add Dewar-pyridine *(79)*[86], the adduct *(80)* between dimethyl acetylenedicarboxylate and cyclooctatetraene[29], as well as the cyclobutadiene complex *(81)*[27,28].

10. Relationship between Cyclobutadiene and Cyclopentadienone

Two *tert*-butyl groups suffice (Section 8) to reduce the reactivity of the cyclopentadienone ring system to such an extent that compounds stable at room temperature are obtained. Since *(36)* and *(37)* have become readily accessible, the properties of these annulenones can now be studied in detail. These investigations are closely related to the cyclobutadiene problem. Any contribution by canonical structure *(36a)* will lead to an antiaromatic destabilization of species *(36)*; if *(36c)* represents the molecule better it will be manifested in a drastic modification of the carbonyl reactivity owing to the reversed polarity of the C=O double bond.

[**] *Note added in proof* (July 8, 1974): Irradiation of anhydride *(73)* in an argon matrix at 8K also results in a clean photocleavage to CO_2, CO, and unsubstituted cyclobutadiene (1237, 653, 573 cm^{-1}) [124].



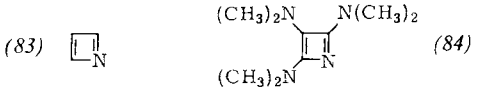
(36a) (36b) (36c)

Thus the cyclopentadienone molecule[90] poses problems[91] resembling those considered for cyclobutadiene in Section 3. Attempted syntheses have been reported on several occasions[92–94]. It was only in 1971[95] that the parent compound could be synthesized and detected by IR spectroscopy at low temperature. Derivatives *(49)*[96], *(37)*[97a], and *(54)*[97b] have so far remained poorly accessible.

Studies performed hitherto on the available substances indicate that the cyclopentadienone ring system possesses the character of a "normal" unsaturated ketone in the electronic ground state (IR, NMR, photoelectron spectra[98]). (A different situation is found in cyclopropenones where conjugative effects are significant[99].) However, the UV spectra[60] of cyclopentadienones warrant attention. The frequency of the long-wave band is highly dependent upon the number and position of the substituents. From a chemical standpoint (carbonyl reactions) they do not behave in a typical manner (no hydrazone formation, *etc.*). It should also be mentioned that on adduct formation between cyclopentadienones and cyclobutadienes the former always act as dienes and the latter exclusively as dienophiles, although the cyclopentadienone certainly has the lower electron density of the two ring systems. These reactions therefore have to be classified as Diels-Alder reactions with inverse electron demands.

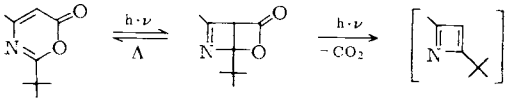
11. Azacyclobutadiene

A compelling analogy exists between azacyclobutadiene *(83)*, the simplest heterocyclobutadiene, and the pure carbocycle *(1)*. Application of the methods discussed so far to the preparation of azacyclobutadienes appears particularly promising since calculations by *Dewar*[100] ascribe a stabilizing effect to the nitrogen [lowering the negative resonance energy from −18 kcal/mol (cyclobutadiene) to −15.5 kcal/mol (azacyclobutadiene); a value of +23.1 kcal/mol is calculated for pyridine]. Additional stabilization is to be expected from donor groups in positions 2 and 4[101]. Hence it becomes clear why *Gompper*[102] was able to isolate the azacyclobutadiene derivative *(84)*.



(83) (84)

Oxazinones of type *(85)*[103] are favorable starting materials for the photochemical generation of the parent compound *(83)* ("azete") or its simply substituted derivatives. We[104] have examined the photochemical behavior of, *inter alia*, compound *(85)* and discovered that irradiation at −78 °C readily yields the bicyclic valence isomer *(86)*[69]. The starting compound *(85)* is regenerated on thawing to room temperature. If the bicyclic lactone is further irradiated at low temperature, elimination of CO_2 can be observed by IR spectroscopy. Since no acetonitrile is formed as cleavage product, it may be concluded that the aza derivative undergoes the desired photocleavage into azacyclobutadiene *(87)* and CO_2, in analogy to the cleavage of the Corey lactone *(78)*. Although structural elucidation of the photoproducts is not yet complete, available evidence would indicate that azacyclobutadienes are amenable to a variety of stabilization reactions. Whereas



(85) (86) (87)

dimerization plays the dominant role in the carbocyclic systems, the situation is more complex in the aza series, possibly because of the high polarity of the C=N double bond.

12. Cyclobutadiene/Tetrahedrane Valence Isomerism

Only two possible structures are open to a compound having the composition $(CH)_4$ (four methine groups), *viz.* cyclobutadiene *(1)* and tetrahedrane *(88)*. Only photochemical transitions between these two valence isomers are "symmetry-allowed"[105]. The fact that thermal isomerization of tetrahedrane to cyclobutadiene is "symmetry-forbidden" provides a ray of hope that it might just be possible to produce a compound having the tetrahedrane structure. Thermodynamically the chances appear very remote: the energy content of tetrahedrane is calculated[106] to exceed that of cyclobutadiene by 70[106a] or 84 kcal/mol[106b]. Moreover, the alternative pathway, primary cleavage to the diradical *(89)*, is predicted to



(1) (88) (89)

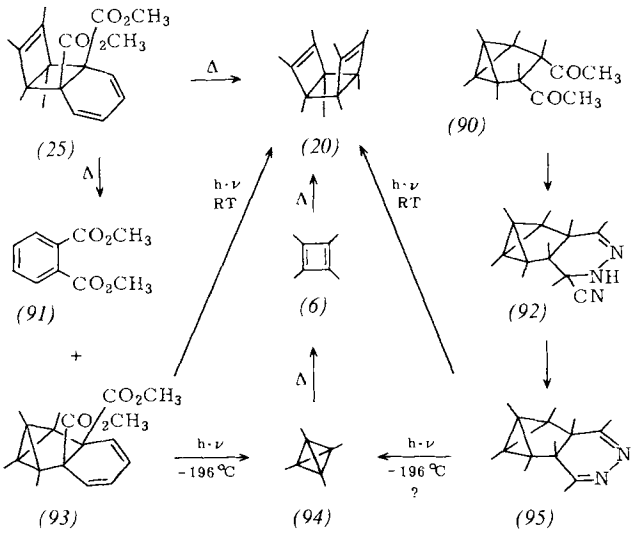
be isothermal[106b]. In other words: this bond rupture must be accompanied by a barrier of more than 20 kcal/mol if tetrahedrane is to be identified as an intermediate trapped in a matrix.

Since theoretical predictions regarding both the energy content of tetrahedrane and the height of the energy barrier for conversion into *(89)* are contradictory[106, 107], only experiments can decide.

There has been no lack of attempts[108]. However, all claims to successful syntheses have so far failed to stand up to scrutiny. The most convincing studies are still those[109–111] in which evidence for the occurrence of a tetrahedrane intermediate is gleaned from the labeling pattern of acetylenes obtained as cleavage products.

It was our objective to gain an indication of whether tetramethyltetrahedrane *(94)* is capable of existence by photocleavage of the bicyclobutane derivatives *(93)* and *(95)*, whose cyclobutene analogs *(25)* and *(17)*, respectively, yield tetramethylcyclobutadiene almost quantitatively on irradiation (Section5). Starting from the diacetyl compound *(90)*[112], the heterocycle *(95)* can be obtained *via* the hydrocyanic acid adduct *(92)*[113]. The second photoprecursor *(93)* results[114] on pyrolysis of the tricyclic compound *(25)*. Unfortunately, the yield of *(93)*

is very low (≈ 1 %). The major products of thermal cleavage are the dimer *(20)* of tetramethylcyclobutadiene and dimethyl phthalate *(91)*, as for photofragmentation.



What can be said about the photochemical behavior of the two potential tetrahedrane precursors *(93)* and *(95)*? Room-temperature irradiation of the heterocycle *(95)* affords[113] a complex product mixture. Apart from octamethylcyclooctatetraene *(18)* and its photoproducts[33], a small amount of the dimer *(20)* can be detected. This finding might be construed as indicating that the reaction does indeed follow the pathway *(95)* → *(94)* → *(6)* → *(20)* to a certain extent.

The results obtained on irradiation of the diester *(93)* are even more exciting[113]. As in the case of the cyclobutene isomer *(25)*, room-temperature irradiation furnishes dimethyl phthalate *(91)* and the dimer *(20)* of tetramethylcyclobutadiene *(6)* almost quantitatively. This observation could indicate that *(93)* initially regenerates *(25)* which then yields the isolated products. Such a conclusion is discounted on the one hand by the failure to detect *(25)* as an intermediate on following irradiation of *(93)*. On the other hand, this possibility is ruled out by the results of matrix irradiation. After irradiation of *(93)* at −196 °C and subsequent warming to room temperature, *(91)* and *(20)* are again the sole products. If *(93)* were to undergo isomerization to the tricycle *(25)* in the initial reaction step, then the maximum corresponding to the charge-transfer complex *(27)* would appear in the low-temperature UV spectrum as discussed in Section 5. However, no such absorption band can be detected.

Thus, in our opinion, it is not tetramethylcyclobutadiene *(6)* which is trapped in the matrix but another species that is readily transformed into *(6)*. It is very tempting to regard this intermediate as tetramethyltetrahedrane *(94)*. If this were the case, then it follows that the tetrahedrane derivative *(94)* is stable in a matrix at −196 °C and undergoes valence isomerization to *(6)* only on thawing to a temperature range in which the matrix is already soft enough to permit dimerization. Since the intermediacy of tetramethylcyclobutadiene *(6)* cannot be detected by spectroscopy, the rate at which the dimer *(20)* is formed must exceed that of valence isomerization *(94)* → *(6)*.

To date we have been unable to decide whether the species frozen into the matrix really is tetramethyltetrahedrane *(94)* or possibly the corresponding bicyclobutanediyl diradical. In any case, we regard the above results as a challenge to defy the theorists' rather gloomy predictions and to persevere in our attempts to solve the tetrahedrane problem too.

13. Summary

What is the current state of our knowledge, *i.e.*, what answers can be given to the questions posed in Section 3?

1) Suitable methods exist for the photochemical generation of cyclobutadiene and its simply substituted derivatives at low temperatures. On irradiation of cyclobutenedicarboxylic anhydrides, cyclopentadienones are formed as coproducts. Heterocyclobutadienes, *e.g.* azacyclobutadiene *(87)*, also appear to be accessible by photofragmentation of suitable precursors.

2) Cyclobutadienes can be obtained as monomers by use of the matrix isolation technique.

3) Evidence exists that cyclobutadienes, and especially higher substituted derivatives, possess a singlet ground state. Thus we have so far been unable to observe the signals expected for a triplet in the ESR spectrum of both the parent system and tetramethylcyclobutadiene. However, this "negative" finding should not be given too much weight. The following chemical argument is perhaps more convincing: Dimerization of cyclobutadienes could, in principle, yield not only *syn* dimers of type *(76)* but also the *anti*-configurated isomers. These stabilization reactions are always strictly stereospecific, however. After thawing of the matrix only one tricycle is found in each case. It may be concluded from the proven *syn* configuration of *(42)*[115] and *(76)*[76] that the other dimers possess an analogous stereochemistry. Assuming that this stereospecificity can only be expected of singlet molecules (*endo* rule of the Diels-Alder reaction), then this finding would also contraindicate a triplet ground state. Nevertheless, it should be mentioned that neither experimental proof nor theoretical explanation can yet be offered. Nobody knows whether a triplet cyclobutadiene might not also be able to form the *syn* adducts in a stereospecific manner. Finally, the photoelectron spectra also point to singlet ground states[73].

4) The IR spectra recorded for unsubstituted cyclobutadiene[13,86-88] are compatible only with a square arrangement. A rectangular geometry or distortions of the kind shown in Figure 2 would lead to a greater number of bands.

5) Cyclobutadienes are characterized by typical UV spectra. Unsubstituted cyclobutadiene and its monosubstituted derivatives display a band at 300—305 nm. In contrast, higher substituted derivatives appear to possess no band above 300 nm. "Free" tetramethylcyclobutadiene displays only a gradual increase from 300 nm towards shorter wavelengths. Tetramethylcyclobutadiene shows an exceptionally pronounced tendency to form charge-transfer complexes with suitable acceptors. Relevant information is available concerning the ionization energies of cyclobutadiene[116] and some of its derivatives[73,117,118]. The good donor properties of tetramethylcyclobutadiene accordingly become understandable.

6) Cyclobutadienes are extremely reactive compounds. Even tri-*tert*-butylcyclobutadiene undergoes relatively rapid trans-

formation into its dimer, even though molecular models indicate considerable steric hindrance in the transition state. Apart from dimerization, autoxidation also appears to be a typical stabilization reaction.

7) Studies on di-*tert*-butyl[36, 60] and diphenylcyclobutadiene[52] provide some evidence for the existence of a valence-isomeric equilibrium. The results available suggest that the energy barrier is not higher than about 8 kcal/mol[12].

8) As required by theory, tetrahedrane is probably even more unstable than its valence isomer. Preliminary studies suggest that tetramethyltetrahedrane is capable of existence when frozen into a matrix, but is transformed extremely readily into tetramethylcyclobutadiene.

9) Quantitative experimental determination of the antiaromatic destabilization of cyclobutadiene has been attempted[15]. It is reported to lie in the range of 12—16 kcal/mol. The extremely high reactivity of cyclobutadienes, exceeding that of cyclopentadienones, for which diffusion-controlled rate constants are discussed, likewise reflects their high energy content. Of course, this argument only applies when the energy of the transition state is not increased to the same extent. However, calculations[12] show that its transition state is considerably less destabilized than cyclobutadiene itself. Reliable information about the π-orbital energies is available from photoelectron spectra. While the ionization potential is estimated as 8.50 eV[25, 116] in unsubstituted cyclobutadiene *(1)*, it amounts to 6.89 eV[73] in the case of *(68)*, and, surprisingly, tri-*tert*-butylcyclobutadiene *(57)* shows a similarly low value of 6.80 eV[117] although it bears only three alkyl substituents.

All these data refer to electroneutral cyclobutadiene. It may be expected that at least the dication[119] or the dianion of cyclobutadiene, the "aromatic" pendants, so to speak, would be more readily preparable than the "antiaromatic" *(1)*. The dications of tetramethylcyclobutadiene[120] and tetraphenylcyclobutadiene[121] have in fact been prepared by *Olah*, and convincing evidence for the existence of cyclobutadiene dianion has been reported by *Pettit*[122].

14. Future Tasks

Questions still remain to be answered. To name but a few: Why does cyclobutadiene react as a singlet molecule although IR spectra prove it to have a square structure, *i.e.* precisely that geometry which theory requires for a triplet ground state? Why do the UV spectra differ from those of more highly substituted derivatives? Is this a consequence of a change in multiplicity depending on the number of substituents? Is it permissible to postulate that the former have a triplet ground state and the latter a singlet ground state on the basis of a comparison with calculated spectra? How can tetramethylcyclobutadiene react as a singlet molecule when generated photochemically at low temperatures, while the same molecule appears to display triplet character at very high temperature[123]?

What kind of barrier determines a valence isomerism of the type *(57a)*$\rightleftharpoons$*(57b)*? What interrelationships describe the cyclobutadiene/tetrahedrane system?

This list could be continued. The points mentioned underline the importance of following the fragmentation of available precursors in noble gas matrices by UV, IR, Raman, and ESR spectroscopy. Correlation of the results obtained should provide unequivocal information. Relevant studies are in progress[124].

Furthermore, gas-phase thermal cleavages of suitable starting materials are necessary in order to determine whether the multiplicity in the ground state changes as a function of temperature. The adducts *(21)*, *(22)*, and *(25)*, which undergo both photochemical and thermal cleavage[41, 114] as already mentioned in Section 12, represent suitable model substances. Fragmentation to tetramethylcyclobutadiene and the corresponding aromatic coproducts already begins at 50 °C. This means that all the prerequisites are now fulfilled for answering the remaining open questions in the near future.

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German version: Angew. Chem. *86*, 491 (1974)

[1] *A. Kekulé*, Liebigs Ann. Chem. *162*, 77 (1872).

[2] *R. Willstätter* and *W. v. Schmaedel*, Ber. Deut. Chem. Ges. *38*, 1992 (1905).

[3] *R. Willstätter* and *E. Waser*, Ber. Deut. Chem. Ges. *44*, 3423 (1911); *R. Willstätter* and *M. Heidelberger*, *ibid. 46*, 517 (1913).

[4] *M. P. Cava* and *M. J. Mitchell*: Cyclobutadiene and Related Compounds. Academic Press, New York 1967.

[5] In addition to the book by *Cava* and *Mitchell* [4], which deals exhaustively with earlier work, a number of other surveys have meanwhile appeared: *P. J. Garratt* and *M. V. Sargent*, Advan. Org. Chem. *6*, 1 (1969); *D. Seebach* in Houben-Weyl: Methoden der Organischen Chemie. Thieme, Stuttgart 1971, Vol. IV/4, pp. 231 ff.; concerning tetramethylcyclobutadiene, cf. *R. Criegee*, Angew. Chem. *74*, 702 (1962); Angew. Chem. internat. Edit. *1*, 519 (1962); a review of stabilized cyclobutadienes and related compounds will appear shortly: *R. Gompper* and *G. Seybold*, Topics in Nonbenzenoid Aromatic Chemistry, in press.

[6] *E. Hückel*: Grundzüge der Theorie ungesättigter und aromatischer Verbindungen. Verlag Chemie, Berlin 1938.

[7] For a summary of earlier theoretical work with a detailed discussion, see: *H. E. Simmons* and *A. G. Anastassiou* in ref. [4], Chapter 12.

[8] a) *M. J. S. Dewar* and *G. J. Gleicher*, J. Amer. Chem. Soc. *87*, 3255 (1965); b) *M. J. S. Dewar*: The Molecular Orbital Theory of Organic Chemistry. McGraw-Hill, New York 1969; c) *M. J. S. Dewar* and *C. de Llano*, J. Amer. Chem. Soc. *91*, 789 (1969).

[9] a) *N. L. Allinger*, *C. Gilardeau*, and *L. W. Chow*, Tetrahedron *24*, 2401 (1968); b) *N. L. Allinger* and *J. C. Tai*, Theor. Chim. Acta *12*, 29 (1968).

[10] *R. J. Buenker* and *S. D. Peyerimhoff*, J. Chem. Phys. *48*, 354 (1968).

[11] *B. A. Hess* and *L. J. Schaad*, J. Amer. Chem. Soc. *93*, 305 (1971); Tetrahedron Lett. *1972*, 5113.

[12] *M. J. S. Dewar*, *M. C. Kohn*, and *N. Trinajstić*, J. Amer. Chem. Soc. *93*, 3437 (1971).

[13] *A. Krantz*, *C. Y. Lin*, and *M. D. Newton*, J. Amer. Chem. Soc. *95*, 2744 (1973).

[14] *H. J. Lindner* and *B. von Gross*, Angew. Chem. *83*, 489 (1971); Angew. Chem. internat. Edit. *10*, 490 (1971).

[15] a) *R. Breslow* and *W. Washburn*, J. Amer. Chem. Soc. *92*, 427 (1970); b) *R. Breslow*, *R. Grubbs*, and *S.-I. Murahashi*, *ibid. 92*, 4139 (1970); c) *R. Breslow*, Pure Appl. Chem. *28*, 111 (1971); d) *R. Breslow*, Accounts Chem. Res. *6*, 393 (1973).

[16] *H. P. Figeys*, Tetrahedron *26*, 5225 (1970).

[17] *M. J. S. Dewar*, Angew. Chem. *83*, 859 (1971); Angew. Chem. internat. Edit. *10*, 761 (1971).

[18] Contributions in a) *E. D. Bergmann* and *B. Pullman*: Aromaticity, Pseudo-Aromaticity, Anti-Aromaticity. The Israel Academy of Sciences and Humanities, Jerusalem 1971; b) *M. Oki*: The Chemistry of Nonbenzenoid Aromatic Compounds. Butterworths, London 1971.

[19] *G. Binsch* in [18a], pp. 25ff.

[20] *R. Weiss* and *J. N. Murrell*, Tetrahedron *27*, 2877 (1971); see also: *R. Hoffmann*, Chem. Commun. *1969*, 240, and ref. [12].

[21] Work by *M. P. Cava*, cited in [4]; cf. also *P. J. Garratt* and *R. H. Mitchell*, Chem. Commun. *1968*, 719.

[22] a) *R. Gompper* and *G. Seybold*, Angew. Chem. *80*, 804 (1968); *83*, 44, 45 (1971); Angew. Chem. internat. Edit. *7*, 824 (1968); *10*, 67, 68 (1971); b) *M. Neuenschwander* and *A. Niederhauser*, Chimia *22*, 491 (1968); Helv. Chim. Acta *53*, 519 (1970).

[23] a) *R. Criegee* and *G. Schröder*, Liebigs Ann. Chem. *623*, 1 (1959); b) *W. Hübel* and *E. H. Braye*, J. Inorg. Nucl. Chem. *10*, 250 (1959); *W. Hübel*, *E. H. Braye*, *A. Clauss*, *E. Weiss*, *U. Krüerke*, *D. A. Brown*, *G. S. D. King*, and *C. Hoogzand*, *ibid. 9*, 204 (1959); c) *G. F. Emerson*, *L. Watts*, and *R. Pettit*, J. Amer. Chem. Soc. *87*, 131 (1965); *J. D. Fitzpatrick*, *L. Watts*, *G. F. Emerson*, and *R. Pettit*, *ibid. 87*, 3254 (1965); *R. G. Amiet*, *P. C. Reeves*, and *R. Pettit*, Chem. Commun. *1967*, 1208; d) *H. D. Scharf* and *K. R. Stahlke*, Angew. Chem. *82*, 835 (1970); Angew. Chem. internat. Edit. *9*, 810 (1970); e) survey: *P. M. Maitlis* and *K. W. Eberius*: Nonbenzenoid Aromatics. Organic Chemistry Volume 16-II, Chap. 6. Academic Press, New York 1971.

[24] *P. H. Li* and *H. A. McGee jr.*, Chem. Commun. *1969*, 592.

[25] *E. Hedaya*, *I. S. Krull*, *R. D. Miller*, *D. W. McNeill*, *P. F. D'Angelo*, and *P. Schissel*, J. Amer. Chem. Soc. *91*, 1875 (1969).

[26] *E. Hedaya*, *R. D. Miller*, *M. E. Kent*, *P. F. D'Angelo*, and *P. Schissel*, J. Amer. Chem. Soc. *91*, 6880 (1969).

[27] *M. J. R. Tyerman*, *M. Kato*, *P. Kebarle*, *S. Masamune*, *O. P. Strausz*, and *H. E. Gunning*, Chem. Commun. *1967*, 497.

[28] *J. Font*, *S. C. Barton*, and *O. P. Strausz*, Chem. Commun. *1970*, 499.

[29] *R. D. Miller* and *E. Hedaya*, J. Amer. Chem. Soc. *91*, 5401 (1969).

[30] Review articles: *H. E. Hallam*, Annu. Rep. Progr. Chem. *67*, 117 (1970); Phys. Blätter *28*, 555 (1972); *H. E. Hallam*: Vibrational Spectroscopy of Trapped Species. Wiley, London 1973.

[31] *B. Meyer*: Low Temperature Spectroscopy. American Elsevier, New York 1971.

[32] *R. Criegee*, *U. Zirngibl*, *H. Furrer*, *D. Seebach*, and *G. Freund*, Chem. Ber. *97*, 2942 (1964).

[33] *G. Maier* and *U. Mende*, Angew. Chem. *80*, 532 (1968); Angew. Chem. internat. Edit. *7*, 537 (1968).

[34] *G. Maier* and *U. Mende*, Tetrahedron Lett. *1969*, 3155.

[35] *G. Maier* and *A. Alzérreca*, unpublished.

[36] *G. Maier*, *G. Fritschi*, and *B. Hoppe*, Angew. Chem. *82*, 551 (1970); Angew. Chem. internat. Edit. *9*, 529 (1970).

[37] *G. Maier* and *U. Mende*, Angew. Chem. *81*, 114 (1969); Angew. Chem. internat. Edit. *8*, 132 (1969); cf. also: *R. Criegee*, *W. Eberius*, and *H.-A. Brune*, Chem. Ber. *101*, 94 (1968).

[38] *G. Maier* and *M. Schneider*, Angew. Chem. *83*, 885 (1971); Angew. Chem. internat. Edit. *10*, 809 (1971).

[39] *G. Maier* and *M. Schneider*, unpublished.

[40] We are grateful to Prof. Dr. *R. Askani*, Universität Giessen, for communication of the procedure for the preparation of the adduct of 1,4-cyclohexadienedicarboxylic anhydride and tetramethylcyclobutadiene.

[41] *G. Maier*, *W. Mayer*, *C. Haacke*, and *R. Askani*, Angew. Chem. *85*, 1057 (1973); Angew. Chem. internat. Edit. *12*, 1016 (1973).

[42] As an additional method one could consider the cleavage of the ozonide of hexamethyl (Dewar benzene): *P. R. Story*, *W. H. Morrison*, and *J. M. Butler*, J. Amer. Chem. Soc. *91*, 2398 (1969); however, this reaction does not proceed cleanly enough.

[43] *M. P. Cava* and *B. Hwang*, Tetrahedron Lett. *1965*, 2297.

[44] *K. V. Scherer* and *T. J. Meyers*, J. Amer. Chem. Soc. *90*, 6253 (1968).

[45] *R. Criegee* and *R. Huber*, Angew. Chem. *81*, 749 (1969); Angew. Chem. internat. Edit. *8*, 759 (1969); Chem. Ber. *103*, 1855, 1862 (1970).

[46] *G. Amiet*, *K. Nicholas*, and *R. Pettit*, Chem. Commun. *1970*, 161.

[47] *G. L. Closs* and *V. N. M. Rao*, J. Amer. Chem. Soc. *88*, 4116 (1966).

[48] *H.-D. Scharf* and *F. Korte*, Angew. Chem. *77*, 452 (1965); Angew. Chem. internat. Edit. *4*, 429 (1965).

[49] *G. O. Schenck*, *W. Hartmann*, and *R. Steinmetz*, Chem. Ber. *96*, 498 (1963).

[50] *G. Maier*, *G. Fritschi*, and *B. Hoppe*, Tetrahedron Lett. *1971*, 1463.

[51] *V. R. Sandel* and *H. H. Freedman*, J. Amer. Chem. Soc. *90*, 2059 (1968), and references cited therein.

[52] *P. Reeves*, *T. Devon*, and *R. Pettit*, J. Amer. Chem. Soc. *91*, 5890 (1969).

[53] *A. Alzérreca*, Diplomarbeit, Universität Karlsruhe 1970.

[54] a) *M. Avram*, *E. Avram*, *G. D. Mateescu*, *I. G. Dinulescu*, *F. Chiraleu*, and *C. D. Nenitzescu*, Chem. Ber. *102*, 3996 (1969); b) *M. Avram*, *I. G. Dinulescu*, *G. D. Mateescu*, *E. Avram*, and *C. D. Nenitzescu*, Rev. Roum. Chim. *14*, 1181 (1969); c) *M. Avram*, *D. Constantinescu*, *I. G. Dinulescu*, and *C. D. Nenitzescu*, Tetrahedron Lett. *1969*, 5215; d) *M. Avram*, *D. Constantinescu*, *I. G. Dinulescu*, *O. Constantinescu-Simon*, *G. D. Mateescu*, and *C. D. Nenitzescu*, Rev. Roum. Chim. *15*, 1097 (1970); e) *M. Avram*, *E. Avram*, *I. G. Dinulescu*, *N. Stefan*, *F. Chiraleu*, *M. Elian*, and *C. D. Nenitzescu*, Chem. Ber. *105*, 2375 (1972).

[55] *E. Müller*, *H. Fettel*, and *M. Sauerbier*, Synthesis *1970*, 82.

[56] *T. Hosokawa* and *I. Moritani*, Tetrahedron Lett. *1969*, 3021, 4836; Chem. Commun. *1970*, 905.

[57] *P. Reeves*, *J. Henery*, and *R. Pettit*, J. Amer. Chem. Soc. *91*, 5888 (1969).

[58] *J. Ciabattoni* and *A. E. Feiring*, J. Amer. Chem. Soc. *94*, 5113 (1972).

[59] We are grateful to Prof. Dr. *R. E. K. Winter*, St. Louis, Missouri (USA), for communication of a procedure for the preparation of *(35)*.

[60] *G. Maier* and *F. Bosslet*, Tetrahedron Lett. *1972*, 1025.

[61] The same anhydride has been prepared independently by Dr. *M. Wiessler*, Heidelberg, to whom we are grateful for a sample of *(48)* and for a procedure for the preparation of 1,2-di-*tert*-butylcyclobutenedicarboxylic anhydride whose photolysis we are currently investigating (experimental work by *C. Haacke*).

[62] *G. Maier* and *F. Bosslet*, Tetrahedron Lett. *1972*, 4483; the structure given therein for the second oxidation product (1,3-di-*tert*-butyl-3-pivaloylcyclopropene) should be replaced by *(66)*.

[63] *E. E. van Tamelen* and *T. H. Whitesides*, J. Amer. Chem. Soc. *93*, 6129 (1971).

[64] *H. Wynberg* and *U. E. Wiersum*, Chem. Commun. *1965*, 1.

[65] *G. Maier* and *A. Alzérreca*, Angew. Chem. *85*, 1056 (1973); Angew. Chem. internat. Edit. *12*, 1015 (1973).

[66] *A. Alzérreca*, Dissertation, Universität Marburg 1974.

[67] *S. Masamune*, *N. Nakamura*, *M. Suda*, and *H. Ona*, J. Amer. Chem. Soc. *95*, 8481 (1973).

[68] *G. Maier* and *F. Bosslet*, unpublished.

[69] We are grateful to Dr. *R. Matusch*, Fachbereich Pharmazie der Universität Marburg, for recording the NMR spectra.

[70] *H. Kimling* and *A. Krebs*, Angew. Chem. *84*, 952 (1972); Angew. Chem. internat. Edit. *11*, 932 (1972).

[71] *G. Wittig* and *J. Weinlich*, Chem. Ber. *98*, 471 (1965).

[72] *D. E. Applequist*, *P. A. Gebauer*, *D. E. Gwynn*, and *L. H. O'Connor*, J. Amer. Chem. Soc. *94*, 4272 (1972).

[73] *G. Lauer*, *C. Müller*, *K.-W. Schulte*, *A. Schweig*, and *A. Krebs*, Angew. Chem., in press.

[74] *W. Hartmann*, Chem. Ber. *102*, 3974 (1969).

[75] a) *G. Maier* and *B. Hoppe*, Tetrahedron Lett. *1973*, 861; b) *B. Hoppe*, Diplomarbeit, Universität Karlsruhe 1970.

[76] *M. Avram*, *I. G. Dinulescu*, *E. Marica*, *G. Mateescu*, *E. Sliam*, and *C. D. Nenitzescu*, Chem. Ber. *97*, 382 (1964).

[77] a) *L. Watts*, *J. D. Fitzpatrick*, and *R. Pettit*, J. Amer. Chem. Soc. *87*, 3253 (1965); *88*, 623 (1966); *E. K. G. Schmidt*, *L. Brener*, and *R. Pettit*, *ibid. 92*, 3240 (1970).

[78] *G. Koltzenburg*, *P. G. Fuss*, and *J. Leitich*, Tetrahedron Lett. *1966*.

[79] *J. I. Brauman* and *W. C. Archie*, J. Amer. Chem. Soc. *94*, 4262 (1972).

[80] *G. Maier* and *T. Sayrac*, unpublished.

[81] *E. J. Corey* and *J. Streith*, J. Amer. Chem. Soc. *86*, 950 (1964).

[82] a) *M. Rosenblum* and *C. Gatsonis*, J. Amer. Chem. Soc. *89*, 5074 (1967); b) *M. Rosenblum*, *B. North*, *D. Wells*, and *W. P. Giering*, *ibid. 94*, 1239 (1972).

[83] a) *W. H. Pirkle* and *M. Dines*, J. Amer. Chem. Soc. *90*, 2318 (1968); b) *W. H. Pirkle* and *L. H. McKendry*, *ibid. 91*, 1179 (1969).

[84] *O. L. Chapman*, *C. L. McIntosh*, and *J. Pacansky*, J. Amer. Chem. Soc. *95*, 244 (1973).

[85] *B. G. S. Pong* and *J. S. Shirk*, J. Amer. Chem. Soc. *95*, 248 (1973).

[86] *O. L. Chapman*, *C. L. McIntosh*, and *J. Pacansky*, J. Amer. Chem. Soc. *95*, 614 (1973).

[87] *C. Y. Lin* and *A. Krantz*, J. C. S. Chem. Comm. *1972*, 1111.

[88] *O. L. Chapman*, *D. De La Cruz*, *R. Roth*, and *J. Pacansky*, J. Amer. Chem. Soc. *95*, 1337 (1973).

[89] *S. Masamune*, *M. Suda*, *H. Ona*, and *L. M. Leichter*, J. C. S. Chem. Comm. *1972*, 1268.

[90] Review of literature prior to 1964: *M. A. Ogliaruso*, *M. G. Romanelli*, and *E. I. Becker*, Chem. Rev. *65*, 261 (1965).

[91] *E. W. Garbisch* and *R. F. Sprecher*, J. Amer. Chem. Soc. *88*, 3434 (1966).

[92] *K. Hafner* and *K. Goliasch*, Chem. Ber. *94*, 2909 (1961).

[93] *C. H. DePuy*, *M. Isaks*, *K. L. Eilers*, and *G. F. Morris*, J. Org. Chem. *29*, 3503 (1964).

[94] *D. C. DeJongh* and *D. A. Brent*, J. Org. Chem. *35*, 4204 (1970).

[95] O. L. Chapman and C. L. McIntosh, Chem. Commun. 1971, 770.

[96] E. W. Garbisch and R. F. Sprecher, J. Amer. Chem. Soc. 88, 3433 (1966); 91, 6785 (1969).

[97] a) U. Krüerke and W. Hübel, Chem. Ber. 94, 2829 (1961); b) C. Hoogzand and W. Hübel, Tetrahedron Lett. 1961, 637.

[98] W. Schäfer, A. Schweig, G. Maier, and T. Sayrac, J. Amer. Chem. Soc. 96, 279 (1974).

[99] W. Schäfer, A. Schweig, G. Maier, T. Sayrac, and J. K. Crandall, Tetrahedron Lett. 1974, 1213.

[100] M. J. S. Dewar and N. Trinajstić, Theor. Chim. Acta 17, 235 (1970).

[101] H.-U. Wagner, Angew. Chem. 85, 920 (1973); Angew. Chem. internat. Edit. 12, 848 (1973).

[102] G. Seybold, U. Jersak, and R. Gompper, Angew. Chem. 85, 918 (1973); Angew. Chem. internat. Edit. 12, 847 (1973). Review of heterocyclobutadienes: R. Gompper and G. Seybold, Topics in Nonbenzenoid Aromatic Chemistry, in press: for a benzo derivative, cf.: B. M. Adger, M. Keating, C. W. Rees, and R. C. Storr, J. C. S. Chem. Comm. 1973, 19.

[103] W. Steglich, E. Buschmann, and O. Hollitzer, Angew. Chem., in press.

[104] G. Maier and U. Schäfer, unpublished; U. Schäfer, Diplomarbeit, Universität Marburg 1974.

[105] R. B. Woodward and R. Hoffmann, Accounts Chem. Res. 1, 17 (1968).

[106] a) R. J. Buenker and S. D. Peyerimhoff, J. Amer. Chem. Soc. 91, 4342 (1969); b) N. C. Baird and M. J. S. Dewar, J. Amer. Chem. Soc. 89, 3966 (1967); J. Chem. Phys. 50, 1262 (1969); c) N. C. Baird, Tetrahedron 26, 2185 (1970).

[107] I. J. Miller, Tetrahedron 25, 1349 (1969).

[108] Surveys: a) H. A. Staab, E. Wehinger, and W. Thorwart, Chem. Ber. 105, 2290 (1972); b) L. T. Scott and M. Jones, Chem. Rev. 72, 181 (1972).

[109] R. F. Peterson, R. T. K. Baker, and R. L. Wolfgang, Tetrahedron Lett. 1969, 4749.

[110] P. B. Sherlin and A. P. Wolf, J. Amer. Chem. Soc. 92, 406, 5291 (1970).

[111] L. B. Rodewald and H.-K. Lee, J. Amer. Chem. Soc. 95, 623, 3084 (1973).

[112] G. Maier and M. Schneider, Angew. Chem. 85, 174 (1973); Angew. Chem. internat. Edit. 12, 162 (1973).

[113] G. Maier and G. Kreiling, unpublished; G. Kreiling, Dissertation, Universität Marburg 1974.

[114] G. Maier and W. Mayer, unpublished; W. Mayer, Dissertation, Universität Marburg 1974.

[115] G. Maier and G. Fritschi, unpublished.

[116] S. D. Worley, Chem. Commun. 1970, 980.

[117] G. Lauer, C. Müller, K.-W. Schulte, A. Schweig, A. Alzérreca, and G. Maier, unpublished.

[118] R. Gompper, F. Holsboer, W. Schmidt, and G. Seybold, J. Amer. Chem. Soc. 95, 8479 (1973).

[119] Regarding energetic considerations, cf.: S. Hünig and H. Pütter, Angew. Chem. 85, 143 (1973); Angew. Chem. internat. Edit. 12, 149 (1973).

[120] G. A. Olah, J. M. Bollinger, and A. M. White, J. Amer. Chem. Soc.

[121] G. A. Olah and G. D. Mateescu, J. Amer. Chem. Soc. 92, 1430 (1970).

[122] J. S. McKennis, L. Brener, J. R. Schweiger, and R. Pettit, J. C. S. Chem. Comm. 1972, 365.

[123] a) P. S. Skell and R. J. Petersen, J. Amer. Chem. Soc. 86, 2530 (1964); b) R. G. Doerr and P. S. Skell, ibid. 89, 3062 (1967); c) D. G. Whitten and W. Berngruber, ibid. 93, 3204 (1971).

[124] Together with H.-G. Hartan; we are indebted to Dr. B. Mann, Fachbereich Physikalische Chemie, Universität Marburg, for his assistance in the construction of the equipment for low-temperature spectroscopy.

Equilibrium and Transport Properties of Low-Melting Salts

By Joachim Richter[*]

An understanding of the physical and chemical phenomena and the structure of salt melts calls not only for kinetic and spectroscopic data but also for systematic studies on the equilibrium and transport properties of individual systems. The present article deals with the activity coefficients, transport numbers, and self-diffusion and interdiffusion coefficients of salt melts, and the results of consistent measurements of these quantities are reported.

1. Introduction

The term salt melts (or more generally electrolyte melts) is applied to inorganic salts (or electrolytes) that dissociate into their ionic constituents in the molten state. A distinction is made between pure molten salts that consist of only one component, *e.g.* $NaNO_3$, and salt melts that consist of two or more components, *e.g.* $NaNO_3+Ca(NO_3)_2$.

Nitrate melts are among the most thoroughly investigated low-melting salt melts. The general discussions below are illustrated by results for the systems $NaNO_3+AgNO_3$ and $LiNO_3+AgNO_3$.

Interest in salt melts has increased rapidly in recent years for two reasons:

The first reason is the increasingly rapid development of a wide range of practical applications for salt melts, *e.g.* in reactor construction, in the remelting of electrolyte slags and other applications in metallurgy, and as effective, very fluid heat exchangers at high temperatures, in the electrolytic isolation of metals or in fuel cells; moreover, increasing numbers of chemical reactions can be carried out with high rates and in high yields in salt melts, and so on.

The second reason for the growing interests in salt melts is the great importance that they have attained in fundamental research. The study of the thermodynamic, kinetic, and spectroscopic properties of these liquids is improving our understanding of the physical and chemical phenomena and of the structure of melts. Though the matter is still under discussion, there is good reason to hope that the structure of salt melts will be easier to understand than that of systems such as $NaNO_3$ in water, *i.e.* systems with a neutral solvent, which

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have much more complicated structures. Fundamental research is being carried out at present in an effort to clarify the structure of salt melts; this necessitates systematic studies on the equilibrium properties and transport phenomena of individual systems.

The modern literature on salt melts dates back to about 1960 (see *e.g.* the monographs[1-5,8], the book of tables[6], and the data collection[7]). The latest findings and results are presented in the series "Advances in Molten Salt Chemistry", the first volume[9] of which appeared in 1971, the second[9] in 1973. The transport properties of salt melts in particular have formed the subject of recent reviews[10,11]. The literature is rounded off by a number of general surveys[12-15].

2. Activity Coefficients

For the thermodynamic description of salt melts, one requires a clear definition of the activity coefficients of all the components present in a system. Proposals have been made by *Temkin*[16], *Forland*[17], and *Flory*[18], but these are not very suitable for a general description because of the models on which they are based. *Haase*[19,20] introduced the general concept of an "ideal electrolyte melt", and defined suitable activity coefficients in *binary* electrolyte melts by means of the equation

$$\ln f_i \equiv \psi_j - \psi_j^{id} \qquad (1)$$

The activity coefficient f_j of the component j is dimensionless, and depends, as usual, on the temperature T, the pressure P, and the composition. ψ_j is an abbreviation for

$$\psi_j \equiv (\mu_j - \mu_{oj})/RT$$

μ_j is the chemical potential of the component j in the mixture, μ_{oj} is the chemical potential of the pure liquid component j, and R is the gas constant. ψ_j^{id} is the corresponding expression for the standardized ideal melt. The standardized ideal mixture is defined by the condition that the melt is completely dissociated, contains no complex ions, and the expression $\psi_i = \ln x_i$ (x_i: true mole fraction of the ionic species i) is valid for every ionic species i. The reference melt can thus be described by measurable quantities such as the stoichiometric mole fractions.

These new activity coefficients have the advantage that they allow the description of the thermodynamic behavior even of complicated melts, *i.e.* melts in which the constituents have different valencies. The logarithms of these activity coefficients can be represented by power series in the mole fraction with *whole-number* exponents, which satisfy the general principles of thermodynamics. The limiting laws for the freezing point depression and for the vapor pressure of salt melts can thus be given in a simple form[21]. Moreover, for a large number of binary systems, the activity coefficients for the two components of these systems (the parameters of their series expansion) can be calculated from the known analytical expression for the additional molar free enthalpy $\bar{G}^E$[22]. The additional functions of the molar free enthalpy, the molar entropy, and the molar enthalpy can also be derived from these series.

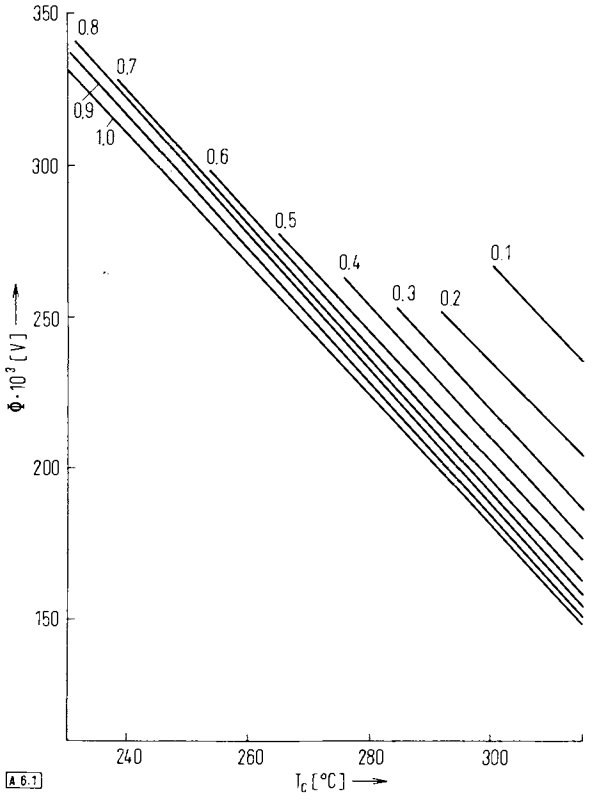


Fig. 1. Emf (Φ) as a function of the temperature T_c for the system $NaNO_3 + AgNO_3$ with the mole fraction x_2 of silver nitrate as the parameter (numbers by the straight lines).

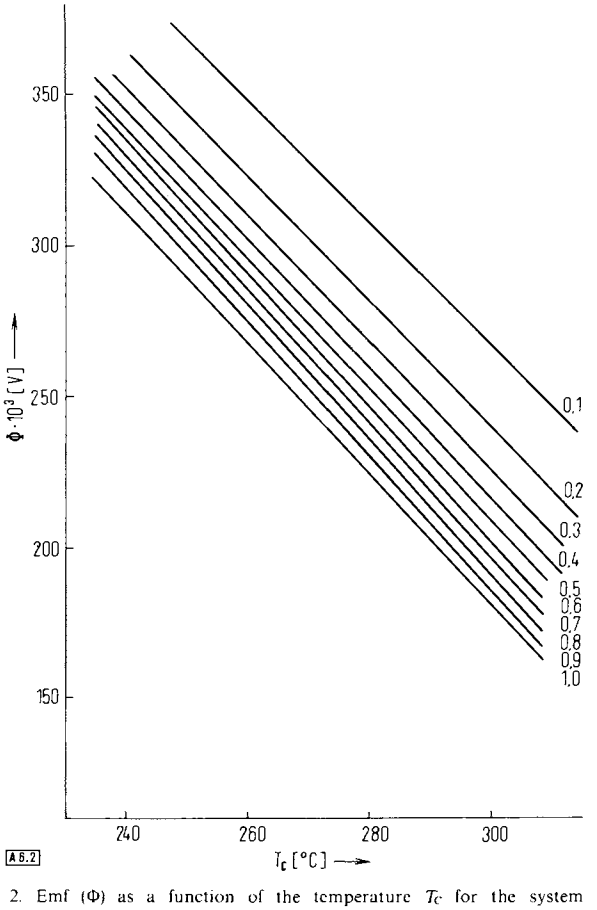


Fig. 2. Emf (Φ) as a function of the temperature T_c for the system $LiNO_3 + AgNO_3$ with the mole fraction x_2 of silver nitrate as the parameter (numbers by the straight lines).

Ketelaar and *Vos*[23] have compared the four definitions of the ideal mixture given by *Temkin*, *Forland*, *Flory*, and *Haase*, and pointed out the differences in the models.

Sehm[24] has recently determined the activity coefficients for the systems $NaNO_3+AgNO_3$ and $LiNO_3+AgNO_3$ in the temperature range 240 to 310 °C over the entire concentration range, as far as the phase diagram allows, by emf measurements on a chemical cell. A nitrate electrode of a form similar to that developed by *Ketelaar* and *Dammers-deKlerk*[25, 26] was used. The measured emf (Φ) is shown as a function of temperature, with the mole fraction of silver nitrate as the parameter, in Figure 1 for the system $NaNO_3+AgNO_3$ and in Figure 2 for the system $LiNO_3+AgNO_3$. Figure 3 shows the activity coefficients calculated from these results for the two systems at fixed temperatures. The interdiffusion coefficients were determined at these temperatures (see Section 5.2 and Fig. 7).

Because of the linear dependence of the emf on the temperature, six constants that are characteristic of the salt melts investigated, and that do not depend either on the composition or on the temperature, can be determined from the analytic presentation of the activity coefficients[27].

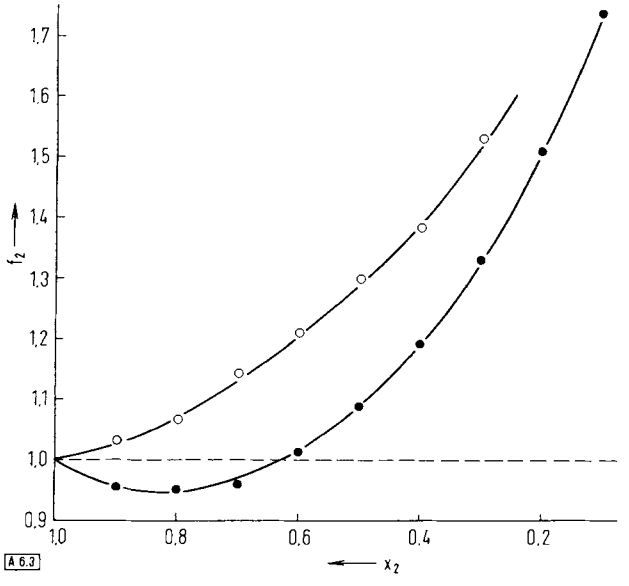


Fig. 3. Activity coefficients f_2 as a function of the mole fraction x_2 of silver nitrate for the system $NaNO_3+AgNO_3$ at 290 °C (o – – o) and for the system $LiNO_3+AgNO_3$ at 260 °C (● — ●).

On the basis of the definition (1), it is possible to derive an expression that enables the activity coefficients of *any* salt melt, regardless of its composition, to be given explicitly. The emf (Φ) of a chemical (isothermally-isobarically reversible) cell obeys the following relation:

$$\ln f_k = \frac{F(\Phi-\Phi_0)}{qRT} - \psi_k^{id} \qquad (2)$$

F is the Faraday constant and Φ_0 is the emf of the cell with the pure component k, for whose ions the electrodes of the cell are reversible. q is the factor that precedes the chemical potential of the component k in the expression for the affinity of the heterogeneous reaction corresponding to k.

The function ψ_j^{id} can now be determined in succession for the individual systems (two components with or without a common ion, *e.g.* $NaNO_3+AgNO_3$ or $NaCl+KBr$, three components with one or two common ions or without a common ion, *e.g.* $NaNO_3+KNO_3+Ca(NO_3)_2$, $NaCl+KCl+KBr$, or $AgCl+TlNO_3+KBr$, *etc.*), and the following rather more complicated expression[28] is found for the general formulation:

$$\psi_j^{id} = \ln \frac{\nu_j^{\nu_j}\prod_{j\alpha}\left[x_j + \sum_{l=1}^{p}(\nu_{l\alpha}/\nu_{j\alpha})x_l\right]^{\nu_{j\alpha}}}{\left(\sum_{i=1}^{n}\nu_i x_i\right)^{\nu_j}} \qquad (3)$$

ν_j is the sum of the dissociation numbers for the component j, x_j is the mole fraction, $\nu_{j\alpha}$ is the dissociation number of the ion α in the component j, and l indicates the components that have an ion in common with the component j. The product in eq. (3) is accordingly taken over the ions of the component j, the summation in l over all p components that have an ion in common with j, and the summation in i over all n components present.

This complicated expression (3) becomes very simple for most of the systems investigated, and together with eq. (2), it allows the determination of activity coefficients from emf measurements for any salt melt, regardless of its composition.

For very simple systems (in which all the components have the same dissociation number and contain a common ion, *e.g.* $KNO_3+AgNO_3+NaNO_3$), this agrees with the usual literature definition, which was taken over from solutions of low molecular weight non-electrolytes:

$$\ln a_j = \ln x_j + \ln \gamma_j$$

In this expression, a_j is the activity and γ_j is the activity coefficient of the component j. The definitions differ in all other cases. The new definition [eqs. (1)—(3)] has the advantage that the logarithm of the activity coefficient for *all* systems can be expanded in series, which are of fundamental importance to all the limiting laws of the salt melts considered.

3. Transport Numbers

The transport numbers are generally determined by three methods, *i.e.* the Hittorf method, the moving boundary method, and emf measurements on concentration cells with transport. The Hittorf method was used for salts melts *e.g.* by *Kawamura* and *Okada*[29], who, like *Duke et al.*[30], used the formula of *Aziz* and *Wetmore*[31] for the evaluation. The question of the external and internal transport numbers (reference systems) and their relation to one another has not yet been clarified here; this problem is being examined at present by *Haase*[32]. The moving boundary method is applied to salt melts only in isolated cases[33], since it is extremely difficult to investigate systems of this type by optical methods. We determined the transport numbers of the systems $NaNO_3+AgNO_3$ and $LiNO_3+AgNO_3$ with the aid of a concentration cell[34].

The concentration cell with transport can be represented for such a system by the following scheme:

$$Cu|Ag|NaNO_3 + AgNO_3(x_I)||NaNO_3 + AgNO_3(x_{II})|Ag|Cu$$

The terminals of the cell, which connect the silver electrodes (Ag) to the measuring instruments, consists of copper. The double line symbolizes the direct liquid contact between the two melts with different concentrations (x_I = mole fraction of silver nitrate in the left half-cell, x_{II} = mole fraction of silver nitrate in the right half-cell). From the emf measured as a function of temperature and composition, the internal transport numbers t_{NA} and t_{Ag} (t_{NO_3} is zero, since the common nitrate ions are reference particles in the sense of the Hittorf reference system) are determined from the following formula[35]:

$$F\Phi = RT\int_{x_I}^{x_{II}} \frac{1}{1-x_2} t_a \, d\ln(x_2/f_2) \qquad (4)$$

x_2 is the mole fraction and f_2 is the activity coefficient of silver nitrate; $t_a = t_{Na}$ or t_{Li}; $t_a + t_{Ag} = 1$. Eq. (4) is evaluated graphically with the aid of the activity coefficients determined by *Sehm*[24] (for further details see[36]). The concentration range in which measurements are possible is $0.7 \leqslant x_2 \leqslant 1.0$ at 240 °C to $0.1 \leqslant x_2 \leqslant 1.0$ at 300 °C for the system $NaNO_3 + AgNO_3$, and $0.1 \leqslant x_2 \leqslant 1.0$ in the same temperature range for the system $LiNO_3 + AgNO_3$. The transport numbers of the systems $NaNO_3 + AgNO_3$ (Fig. 4) and $LiNO_3 + AgNO_3$ (Fig. 5) are shown as examples at the same temperatures as for the activity coefficients (Fig. 3).

Our values are compared in Figure 4 with data found by *Duke et al.*[30] with a Hittorf apparatus. The temperature control was improved in the emf measurements; an analysis *after* the experiment is unnecessary, and the emf apparatus, unlike the Hittorf apparatus used by *Duke et al.*, contains no membrane. The deviation of the transport numbers from the previously found linearity with respect to the mole fraction thus seems to be verified.

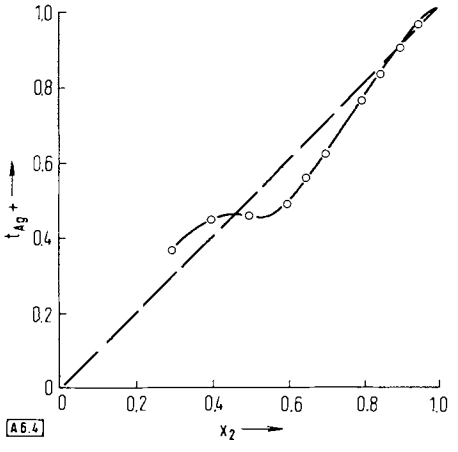


Fig. 4. Transport numbers t_{Ag^+} of the silver ions as a function of the mole fraction x_2 of silver nitrate for the system $NaNO_3 + AgNO_3$. (---): at 305 ± 5 °C (after [30]); (o ··· o): at 290 ± 1 °C.

Figure 5 shows a comparison of the transport numbers for the system $LiNO_3 + AgNO_3$ with the results of Hittorf measurements by *Kawamura* and *Okada*[29], for which the above remark is valid.

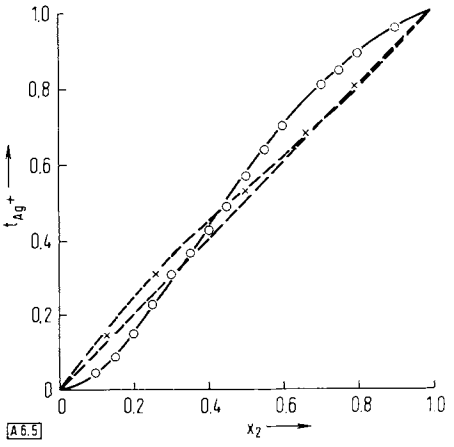


Fig. 5. Transport numbers t_{Ag^+} of the silver ions as a function of the mole fraction x_2 of silver nitrate for the system $LiNO_3 + AgNO_3$. (× ··· ×): at 300 °C (after [29]); (o ··· o): at 260 °C.

From these transport numbers, together with the known densities and electric conductivities of the systems, it is possible to calculate the ion mobilities, equivalent conductivity, and ionic conductivities, as well as their limiting values and values for the ideal melt, as suggested in the papers by *Timmermann* and *Richter*[37] and by *Amkreutz*[36] and calculated for the systems discussed here.

4. Self-Diffusion

4.1. General and Definitions

Investigations on salt melts have so far been confined to the phenomenon of self-diffusion, apart from the few exceptions of interdiffusion (see Section 5). The starting assumption is that the simplest relations between the mobilities and radii of the ions and the structure of the melt are to be expected in self-diffusion, *i.e.* "in the limiting case in which the difference between two diffusing substances in a binary mixture disappears[38]" (the exact definition of self-diffusion is given below), since the measurements are carried out in very simple systems (usually one-component systems) with few assumptions. Moreover, self-diffusion experiments are easier and much faster to carry out than interdiffusion experiments (see Section 5).

The term diffusion is used in general for any mass transport in a mixture that is caused by a concentration gradient. The collective term self-diffusion in particular, which we shall have to differentiate below, is applied to the transport of a labeled ionic species in relation to the same unlabeled ionic species in a salt or in a salt mixture at a concentration gradient close to zero for the labeled particles.

For the definition of self-diffusion, it is necessary to clarify three terms that have been adopted in the literature, *i.e.* tracer diffusion, intradiffusion, and self-diffusion.

Let us first consider a melt that consists of one component, *i.e.* of two ionic constituents, *e.g.* molten sodium chloride with the component NaCl and the two ionic constituents Na and Cl. If we replace some of the Na^+ ions by labeled Na^{+*} ions (experimentally by addition of a radioactive isotope), we have a system for which all three phenomena can be defined.

The diffusion flow density, *i.e.* the quantity of substance passing through a reference surface per unit area and per unit

time, can be defined in any desired reference system. For experimental purposes, we observe the transport of the labeled constituent in relation to the unlabeled constituent. The movements are therefore coupled by the experimental conditions. However, we determine the mean velocity of the ionic constituent with respect to the chosen reference velocity. For simplicity, we consider the one-dimensional case of diffusion (position coordinate z) in the Fick reference system.

In *tracer diffusion*, the reference velocity for the diffusion flow density ${}_w\vec{J}_j^*$ of the labeled ionic component j* (with molarity c_j^*) in the Fick reference system, *i.e.* the mean volume velocity $\vec{w}$, is given by:

$${}_w\vec{J}_j^* = c_j^*(\vec{v}_j^* - \vec{w}) \tag{5}$$

$\vec{v}_j^*$ is the mean velocity of the labeled ionic constituent j*.

Experience shows that each independent diffusion flow is a homogeneous linear function of all the independent concentration gradients if extremely high gradients are ruled out[39]. For the salt melt considered here, it follows that the diffusion flow density defined in eq. (5) is:

$${}_w\vec{J}_j^* = -D_j^* \frac{\partial c_j^*}{\partial z} \tag{6}$$

The tracer diffusion coefficient D_j^* is defined by eq. (6). The operator $\partial/\partial z$ means differentiation with respect to the position coordinate z for a fixed time. The temperature and pressure are the same for all positions (other transport phenomena, such as thermal diffusion, would otherwise occur). Tracer diffusion is thus the diffusion of the labeled ionic constituents in relation to the Fick (or any other chosen) reference system. The tracer diffusion is measured with radioactive isotopes that differ in their physical and chemical behavior from the unlabeled ionic constituents.

If one stipulates that the differences between the chemical properties of the labeled and the unlabeled ionic constituents are negligible, the tracer diffusion will be identical with the *intradiffusion* postulated by *Albright* and *Mills*[40]. These authors introduced the concept of intradiffusion because of the difference between and the ambiguity of the terms tracer diffusion and self-diffusion. However, since intradiffusion cannot be brought about experimentally in the strict sense of its definition, the additional concept of intradiffusion, in my opinion, leads to further confusion. The intradiffusion coefficient is numerically equal to the tracer diffusion coefficient if the differences between the chemical properties of the labeled and of the unlabeled ions disappear.

In tracer diffusion, the concentration of the labeled ions is very low. The labeled ions do not interact directly with one another, or, as formulated by *Bearman*[41], the labeled ions move in an essentially homogeneous environment. The tracer diffusion coefficient nevertheless depends on the concentration of the labeled ions. The hypothetical intradiffusion coefficient, because of the chemical identity of the two ionic species, is independent of the ratio between the concentrations of the labeled and the unlabeled ions, and depends only on the total concentration of the ionic constituent observed.

The *self-diffusion coefficient* D_{ii} of the ionic component i (the same as j, but unlabeled) will be taken here as the limiting value of the tracer diffusion coefficient for a vanishingly small concentration of the labeled ionic constituent j*:

$$D_{ii} \equiv \lim_{c_j^* \to 0} D_j^* = D_{jj} \tag{7}$$

This is found experimentally by measurement of D_j^* as a function of c_j^* and extrapolation to $c_j^* \to 0$. This is the same as saying that the difference in the chemical *and* physical properties disappears.

We can see that self-diffusion does *not* become identical with intradiffusion, since intradiffusion allows differences in the physical properties, *i.e.* in particular in the masses of the isotopes. Analogous isotope effects in the mobilities were carefully investigated by *Lundén* and *Ljubimov*[42] for the system $Li_2SO_4 + K_2SO_4$. These authors defined a mass effect (relative difference in mobility divided by the difference between the masses of the isotopes) and determined its dependence on the composition. It was found that the isotope effects cannot be disregarded.

In the remainder of this discussion, therefore, we shall consider only tracer diffusion and self-diffusion as its limiting value in the sense defined above.

Tracer diffusion and self-diffusion are defined in the same way in aqueous electrolyte solutions and in non-electrolyte solutions[43]. In non-electrolyte solutions, the self-diffusion of the solute at infinite dilution must be physically identical with the interdiffusion (see Section 5). *Bearman*[41] showed that for simple systems of binary non-electrolyte solutions, the interdiffusion coefficient becomes equal to the self-diffusion coefficient at infinite dilution. We were able to show the same result for simple binary salt melts[44].

4.2. Experimental Methods for the Measurement of Self-Diffusion

The most suitable method for the determination of self-diffusion in salt melts is the capillary method, which is the method most commonly used in the investigations. The capillary method exists in two variants. In one case (method 1), a capillary closed at one end and filled with labeled ions is introduced into a bath containing unlabeled salt; in the second variant (method 2), the capillary contains the unlabeled salt, while the bath contains the labeled ions. Method 1 (diffusion out of a capillary) was introduced by *Dworkin et al.*[45] for salt melts; method 2 (diffusion into a capillary) was devised by *Bockris* and *Hooper*[46].

Instead of the capillary, a sintered plate with fine pores may be impregnated with labeled ions and introduced into a bath containing unlabeled salt (method 3). This method (porous frit technique) was devised by *Djordjevic* and *Hills*[47] for salt melts, and developed further by *Sjöblom*[48].

There have been a number of experiments in which a layer of labeled salt was applied over unlabeled salt in a capillary; unlike in methods 1 and 2, therefore, the boundary is situated inside the capillary (method 4). This method, which was introduced by *Angell* and *Bockris*[49] and further developed by *Wallin*[50], is now no longer used.

Finally, *Ketelaar* and *Honig*[51,52] developed the paper electrophoresis method (method 5), in which glass-fiber paper is

Table 1. Self-diffusion coefficients D_{Na^+} in $NaNO_3$ (molten) at 350 C. For methods 1, 2, 3, and 5 see text.

Method	$D_{Na^+} \cdot 10^9$ [$m^2 s^{-1}$]	Ref.
1	2.33 ± 0.04	[45]
1	2.27 ± 0.07	[55]
1	2.27 ± 0.07	[56]
2	2.10 ± 0.09	[57]
2	2.13 ± 0.05	[58]
3	2.44 ± 0.1	[47]
5	2.49 ± 0.1	[52]

impregnated with the salt melt and supported on a glass plate. The tracer diffusion coefficients are then calculated from the Gaussian distribution obtained after a certain time as a result of the diffusion of the radioactive isotopes. In an improvement of this method introduced by *Ketelaar* and *Kwak*[53] in 1967, the glass fiber paper is replaced by quartz glass fibers, and an Al_2O_3 substrate is used as the support. This avoids the exchange of the Na^+ ions in the $NaNO_3$ melt under investigation with the ions in the glass.

As a comparison of the five methods, Table 1 shows the self-diffusion coefficients of Na^+ in $NaNO_3$ at 350 °C as found by seven groups of authors[54]. Method 4 is unsuitable for nitrate melts, and does not therefore appear in Table 1. As has also been observed in measurements on other systems, method 2 gives slightly lower values, and methods 3 and 5 slightly higher values, than method 1. We shall not consider the errors of the individual methods in detail, but merely note that the capillary method has been found to be the best for salt melts.

Another suitable method for the experimental study of self-diffusion is NMR spectroscopy, whose application to salt melts is still in its early stages because of experimental difficulties.

The first investigation on self-diffusion in salt melts was published by *Klemm* and *Berne*[59] in 1953. The authors used the capillary method to investigate the diffusion of radioactive thallium ions in thallium chloride. Very many investigations of self-diffusion in salt melts and above all in metals and metal alloys have now been carried out. (See in particular Refs. [45, 53, 56, 60–64], which are concerned with the nitrate melts discussed here or with their components.)

The most reliable values for the self-diffusion coefficient D_{Na^+} of Na^+ in $NaNO_3$ appear to be those given by *Bockris* and *Nagarajan*[65], which are shown in Table 2 as a function of the temperature T_C.

Table 2. Self-diffusion coefficients D_{Na^+} of Na^+ in $NaNO_3$ as a function of the temperature T_C [65].

T_C [C]	$D_{Na^+} \cdot 10^9$ [$m^2 s^{-1}$]
350	2.14
370	2.38
390	2.61
420	3.04

5. Interdiffusion

5.1. Fundamental Principles

The transport process referred to in normal scientific usage as diffusion will be referred to here as interdiffusion, to distinguish it from self-diffusion. Whereas self-diffusion is investigated mainly in one-component systems, interdiffusion can only occur in systems containing two or more components. Self-diffusion in salt melts has been extensively studied both theoretically and experimentally; on the other hand, the development of experimental methods for the investigation of interdiffusion is still in its early stages.

The theoretical treatment of interdiffusion is particularly simple for salt melts in which two ionic constituents migrate independently of each other in relation to a third. In the following discussion we shall again consider the systems $NaNO_3 + AgNO_3$ and $LiNO_3 + AgNO_3$, which consist of three ionic constituents or of two components in the sense of the Gibbs phase rule with a common anion. In both systems, the cations of the component 1 (Na^+ or Li^+) and the cations of the component 2 (Ag^+) move in relation to the common anion (NO_3^-). This situation is illustrated schematically in Figure 6.

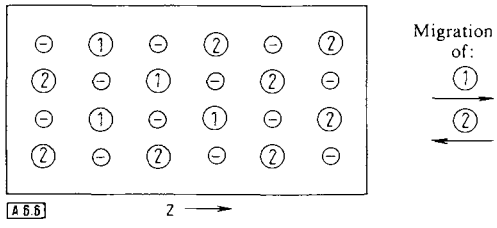


Fig. 6. Schematic representation of a salt melt consisting of two components with a common anion. z = position coordinate. ① denotes the cationic constituent of component 1, ② that of component 2, and ⊖ the common anionic constituent.

In the measurements, the movement of one cation is observed in relation to that of the other. The movements of the two types of cation are thus coupled by the experimental conditions; in this sense, they are not independent of each other. For this reason there is only one interdiffusion coefficient for each system.

This interdiffusion coefficient D can be defined by a generalization of the Fick law[66]:

$$ {}_{\omega}\vec{J}_n = - D \frac{1-\omega_n}{\bar{V}(1-x_n)} \operatorname{grad} x_n \qquad (n=1, 2) \tag{8} $$

${}_{\omega}\vec{J}_n$ is the diffusion flow density of the component n in an arbitrary reference system with the reference velocity $\vec{\omega}$, ω_n are the corresponding weight factors, and $\bar{V}$ is the molar volume of the melt. D is retained in this type of definition in every reference system. As we showed earlier[67], this is possible *only* for salt melts with three ionic constituents. [With this choice of definition, we no longer have the difficulty of converting D^V into D^M (D^V: diffusion coefficient in the Fick reference system, D^M: diffusion coefficient in the barycentric system) *etc.*, which is usually found in the literature.]

The only reference systems of any appreciable importance for diffusion in salt melts are the Fick system and the Hittorf system.

Fick's law[8] in the Fick reference system (index w) has the form:

$$ {}_{w}\vec{J}_2 = - D \frac{V_1}{\bar{V}^2} \operatorname{grad} x_2 \tag{9} $$

V_1 is the partial molar volume of component 1. The corresponding equation in the Hittorf reference system (index $-$), with the mean velocity of the common anionic constituent as the reference velocity, is[67]:

$$-\bar{J}_2 = -\frac{D}{\bar{V}} \frac{1}{x_1 + (\nu_{2-}/\nu_{1-})x_2} \operatorname{grad} x_2 \qquad (10)$$

ν_{1-} and ν_{2-} are the dissociation numbers of the anionic constituents of components 1 and 2.

Fick's second law or a relation corresponding to Fick's second law and following from Fick's first law in the form (9) or (10) is used in the majority of diffusion experiments.

5.2. Experimental Methods for the Measurement of Interdiffusion

Four methods have so far been developed for the investigation of interdiffusion in salt melts. However, all these methods embrace only a very small concentration range, so that they are only suitable for the investigation of the limiting values of the diffusion coefficients for $x_n \rightarrow 0$. *Sjöblom*[63,68] developed a gravimetric method, *Gustafsson et al.*[69,70] an optical method, *Laity* and *Miller*[71] a method that involves the use of a diaphragm cell, and *Thalmayer et al.*[72] a chronopotentiometric technique. *Sjöblom*[73] has now improved the gravimetric method so that measurements are possible over the entire concentration range.

We have modified the method involving the diaphragm cell in such a way that the interdiffusion coefficients of low-melting salt mixtures can be determined relatively accurately over the entire concentration range with the aid of a new evaluation procedure[74]. The results for the system $NaNO_3+AgNO_3$ at 290 °C and for the system $LiNO_3+AgNO_3$ at 260 °C are shown in Figure 7.

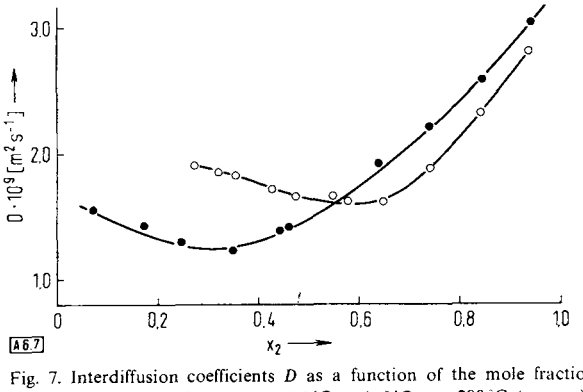


Fig. 7. Interdiffusion coefficients D as a function of the mole fraction x_2 of silver nitrate for the system $NaNO_3+AgNO_3$ at 290 °C (o — o) and for the system $LiNO_3+AgNO_3$ at 260 °C (• — •).

Though the measuring accuracy is relatively good in these investigations, optical methods will probably prove, after further development, to be the best methods for the investigation of diffusion in salt melts, owing to the greater fundamental accuracy of measurement.

6. Closing Remarks

For a deeper understanding of the physical and chemical phenomena and the structure of salt melts, spectroscopic and above all kinetic data are necessary in addition to knowledge of the thermodynamic properties. We confine ourselves here to the thermodynamic data, which include not only those discussed already but also *e.g.* the transport coefficients of the melts in centrifugal and gravity cells[75,76] and in thermopiles[35,77]. The latter are being determined at present in our laboratory for the systems examined here.

A possibility for the unified presentation of the data discussed here is offered by the formalism of the coefficients of friction, as formulated *e.g.* by *Klemm*[78]. This allows one first to calculate the interfriction coefficients, which are a measure of the interactions between different ionic constituents. From these interfriction coefficients, with a very simple assumption about the relationship between self-diffusion and interdiffusion[79], it is possible to calculate the self-friction coefficients, which are a measure of the interactions between similar ionic constituents.

For the binary nitrate melts examined here, therefore, we obtain a total of six friction coefficients for each system.

The transport processes investigated are largely determined by the structure of the salt melt. There are several models for the structure of simple salt melts, which proceed from the experimentally based requirement that a salt melt must contain cavities. The various approaches differ in the interpretation of the size, mode of formation, and distribution of these cavities in the melt, and lead to the quasi-lattice model, to the hole model, to the crystallite or polyhedral hole model, and to the free volume model as described by *Sundheim*[3] for salt melts. These models are rarely discussed nowadays, since they are not very specific and they give a sufficiently good description of the transport properties only with simplifying assumptions.

The models of *Temkin*[16], *Førland*[17], and *Flory*[18] and *Hasse*'s definition[19,20] are based on purely thermodynamic considerations, and formulate the reference melt idealized in some form (ideal behavior of the melt). By themselves, these do not provide evidence of the true structure of a salt melt.

An entirely new development is appearing at present as a result of model calculations using the computer simulation technique, which are yielding the first good results (cf. *e.g.* Ref.[80]).

Optical measurements are necessary in addition to transport and friction coefficients, since the existence of compounds or complexes in the melt cannot be conclusively demonstrated by thermodynamic measurements alone. When the investigations on the transport coefficients of thermal diffusion have been completed, we may obtain a more accurate picture of the structure of low-melting salts.

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[1] *Y. K. Delimarskii* and *B. F. Markov*: Electrochemistry of Fused Salts. Sigma Press, Washington 1961.

[2] *M. Blander*: Molten Salt Chemistry. Interscience, New York 1964.

[3] *B. R. Sundheim*: Fused Salts. McGraw-Hill, New York 1964.

[4] *J. Lumsden*: Thermodynamics of Molten Salt Mixtures. Academic Press, London 1966.

[5] *H. Bloom:* The Chemistry of Molten Salts. Benjamin, New York 1967.

[6] *G. J. Janz:* Molten Salts Handbook. Academic Press, New York 1967.

[7] *G. J. Janz, F. W. Dampier, G. R. Lakshminarayanan, P. K. Lorenz,* and *R. P. T. Tomkins:* Molten Salts. US Dept. of Commerce, National Bureau of Standards, 1968. Vol. I: NSRDS – NBS – 15, Vol. II: SSRDS – NBS – 18.

[8] *G. Mamantov:* Molten Salts. Dekker, New York 1969.

[9] *J. Braunstein, G. Mamantov,* and *G. P. Smith:* Advances in Molten Salt Chemistry. Vol. I. Plenum Press, New York 1971; Vol. II, 1973.

[10] *J. L. Copeland:* Transport Properties of Ionic Liquids. Gordon and Breach, New York 1971.

[11] *C. T. Moynihan* in *S. Petrucci:* Ionic Interactions: From Dilute Solutions to Fused Salts. Vol. I. Academic Press, New York 1971.

[12] *G. E. Blomgren* and *E. R. Van Artsdalen,* Ann. Rev. Phys. Chem. *11*, 273 (1960).

[13] *O. J. Kleppa,* Ann. Rev. Phys. Chem. *16*, 187 (1965).

[14] *S. J. Yosim* and *H. Reiss,* Ann. Rev. Phys. Chem. *19*, 59 (1968).

[15] *C. A. Angell,* Ann. Rev. Phys. Chem. *22*, 429 (1971).

[16] *M. Temkin,* Acta Physicochim. URSS *20*, 411 (1945).

[17] *T. Forland,* Norg. Tek. Vitenskapsakad. Ser. 2, No. 4 (1957).

[18] *P. J. Flory,* J. Chem. Phys. *10*, 51 (1942).

[19] *R. Haase,* Z. Phys. Chem. (Frankfurt) *63*, 95 (1969).

[20] *R. Haase,* J. Phys. Chem. *73*, 1160 (1969).

[21] *J. Richter,* Ber. Bunsenges. Phys. Chem. *72*, 681 (1968).

[22] *J. Richter,* Z. Naturforsch. *24a*, 835 (1969).

[23] *J. A. A. Ketelaar* and *B. Vos,* Monatsh. Chem. *102*, 1284 (1971).

[24] *S. Sehm.* Dissertation, Technische Hochschule Aachen 1971.

[25] *J. A. A. Ketelaar* and *A. Dammers-deKlerk,* Rec. Trav. Chim. Pays-Bas *83*, 322 (1964).

[26] *J. A. A. Ketelaar* and *A. Dammers-deKlerk,* Proc. Kon. Ned. Akad. Wetensch. *B 68*, 169 (1965).

[27] *J. Richter* and *S. Sehm,* Z. Naturforsch. *27a*, 141 (1972).

[28] *J. Richter,* Z. Naturforsch. *24a*, 447 (1969).

[29] *K. Kawamura* and *M. Okada,* Electrochim. Acta *16*, 1151 (1971).

[30] *F. R. Duke, R. W. Laity,* and *B. Owens,* J. Electrochem. Soc. *104*, 299 (1957).

[31] *P. M. Aziz* and *F. E. W. Wetmore,* Can. J. Chem. *30*, 779 (1952).

[32] *R. Haase,* Z. Naturforsch. *28a*, 1897 (1973).

[33] *F. R. Duke* and *J. P. Cook,* Iowa State Coll. J. Sci. *33*, 81 (1958).

[34] *J. Richter* and *E. Amkreutz,* Z. Naturforsch. *27a*, 280 (1972).

[35] *R. Haase* and *J. Richter,* Z. Naturforsch. *24a*, 418 (1969).

[36] *E. Amkreutz.* Dissertation, Technische Hochschule Aachen 1971.

[37] *E. O. Timmermann* and *J. Richter,* Z. Naturforsch. *26a*, 1717 (1971).

[38] *W. Jost:* Diffusion in Solids, Liquids, Gases. Academic Press, New York 1952.

[39] *R. Haase:* Thermodynamik irreversibler Prozesse. Steinkopff, Darmstadt 1963; Thermodynamics of Irreversible Processes. Addison-Wesley, London (1969).

[40] *J. G. Albright* and *R. Mills,* J. Phys. Chem. *69*, 3120 (1965); *72*, 11 (1968).

[41] *R. J. Bearman,* J. Phys. Chem. *65*, 1961 (1961).

[42] *A. Lundén* and *V. Ljubimov,* Z. Naturforsch. *23a*, 1558 (1968).

[43] *H. J. V. Tyrrel:* Diffusion and Heat Flow in Liquids. Butterworth, London 1961.

[44] *J. Richter,* Ber. Bunsenges. Phys. Chem., in press.

[45] *A. S. Dworkin, R. B. Escue,* and *E. R. Van Artsdalen,* J. Phys. Chem. *64*, 872 (1960).

[46] *J. O'M. Bockris* and *S. W. Hooper,* Disc. Faraday Soc. *32*, 218 (1961).

[47] *S. Djordjevic* and *H. J. Hills,* Trans. Faraday Soc. *56*, 269 (1960).

[48] *C.-A. Sjöblom,* Dissertation, Chalmers University, Göteborg 1968.

[49] *C. A. Angell* and *J. O'M. Bockris,* J. Sci. Instrum. *35*, 458 (1958).

[50] *L.-E. Wallin,* Z. Naturforsch. *17a*, 191, 195 (1962).

[51] *E. P. Honig,* Dissertation, University of Amsterdam 1964.

[52] *J. A. A. Ketelaar* and *E. P. Honig,* J. Phys. Chem. *68*, 1596 (1964).

[53] *J. A. A. Ketelaar* and *J. C. Kwak,* J. Phys. Chem. *71*, 1149 (1967).

[54] *C. A. Angell* and *J. W. Tomlinson,* Trans. Faraday Soc. *61*, 2312 (1965).

[55] *F. Lantelme* and *M. Chemla,* Bull. Soc. Chim. *30*, 969 (1963).

[56] *C. A. Angell* and *J. W. Tomlinson,* Disc. Faraday Soc. *32*, 237 (1961).

[57] *J. O'M. Bockris, S. V. Tricklebank,* and *L. Nanis,* Rev. Sci. Instrum. *35*, 807 (1964).

[58] *J. O'M. Bockris, M. K. Nagarajan,* and *L. Nanis,* J. Phys. Chem. *68*, 2726 (1964).

[59] *A. Klemm* and *E. Berne,* Z. Naturforsch. *8a*, 400 (1953).

[60] *E. R. Van Artsdalen, D. Brown, A. S. Dworkin,* and *F. J. Miller,* J. Amer. Chem. Soc. *78*, 1772 (1956).

[61] *C. A. Angell,* J. Phys. Chem. *69*, 399 (1965).

[62] *J. A. A. Ketelaar* and *E. P. Honig,* Trans. Faraday Soc. *62*, 190 (1966).

[63] *C.-A. Sjöblom,* Z. Naturforsch. *20a*, 1572 (1965).

[64] *C.-A. Sjöblom* and *J. Andersson,* Z. Naturforsch. *21a*, 276 (1966).

[65] *J. O'M. Bockris* and *M. K. Nagarajan,* J. Phys. Chem. *70*, 1854 (1966).

[66] *R. Haase* and *M. Siry,* Z. Phys. Chem. (Frankfurt) *57*, 56 (1968).

[67] *J. Richter,* Z. Naturforsch. *25a*, 373 (1970).

[68] *C.-A. Sjöblom* and *A. Behn,* Z. Naturforsch. *23a*, 1774 (1968).

[69] *S. E. Gustafsson, L. E. Wallin,* and *T. E. G. Arvidsson,* Z. Naturforsch. *23a*, 1261 (1968).

[70] *S. E. Gustafsson, T. E. G. Arvidsson,* and *S. A. Afsenius,* J. Chem. Phys. *53*, 2621 (1970).

[71] *R. W. Laity* and *M. P. Miller,* J. Phys. Chem. *68*, 2145 (1964).

[72] *C. E. Thalmayer, S. Bruckenstein,* and *D. M. Gruen,* J. Inorg. Nucl. Chem. *26*, 247 (1964).

[73] *C.-A. Sjöblom, D. Andreasson,* and *A. Behn,* Z. Naturforsch. *25a*, 700 (1970).

[74] *J. Richter,* Z. Naturforsch. *28a*, 492 (1973).

[75] *P. Duby* and *E. Townsend, Jr.,* J. Electrochem. Soc. *115*, 605 (1968).

[76] *J. Richter,* Z. Naturforsch. *25a*, 1757 (1970).

[77] *B. R. Sundheim* and *J. D. Kellner,* J. Phys. Chem. *69*, 1204 (1965).

[78] *A. Klemm,* Z. Naturforsch. *8a*, 397 (1953); *17a*, 805 (1962).

[79] *J. Richter,* unpublished work.

[80] *L. V. Woodcock* in: The Applications of Computer Techniques in Chemical Research. The Institute of Petroleum, London W1M 8AR, 1972.

Transition to Nonmetallic Behavior in Expanded Liquid and Gaseous Metals

By Friedrich Hensel[*]

At high temperatures and pressures, liquid and gaseous metals exhibit a steady transition from metallic to nonmetallic behavior when the density is sufficiently reduced. All the properties are influenced by this transition, as is shown by measurement (on mercury, cesium, and potassium) of the electric conductivity, the density, the thermoelectric power, and in some cases the Hall effect, as well as the optical absorption. The continuous variation of the density over a wide range is achieved by compression or expansion above the critical temperatures of the metals, *i. e.* 1490 °C for mercury, 1750 °C for cesium, and 1925 °C for potassium.

1. Introduction

In a series of liquid and solid solutions of metals in nonmetallic solvents, the solution exhibits a steady transition to metallic conductivity and metallic optical absorption with increasing metal concentration. Examples that have been known for a long time are solutions of alkali metals in liquid ammonia or amines[1-3], solutions of electropositive metals in their molten halides[4, 5], and highly doped solid semiconductors[6]. All these systems, in which the transition from nonmetallic to metallic behavior is brought about by the increasing proximity of the dissolved metal atoms as their concentration is increased, have the disadvantage that they are multicomponent systems. It is therefore necessary to take into account the influence of the solvent, *i. e.* the main component, in the theoretical and experimental study of the transition.

In recent years, metal-nonmetal transitions have also been studied in single-component systems consisting of compressed metal vapors[7-12]. However, a continuous increase in density to the desired degree is possible only if the compression is carried out above the critical temperature. The situation is therefore very similar to that in the solutions of metal in ammonia, in which the transition is also observed only at relatively high temperatures, *i. e.* above the critical temperature T_c of the miscibility gap. Below T_c, two liquid phases coexist, *i.e.* a blue nonmetallic phase and a bronze-colored metallic phase.

Figure 1 shows the equilibrium diagram found experimentally for liquid and gaseous mercury[8, 9, 13]. Here again, phase separation into a vapor having a low density and a relatively low electric conductivity and a liquid having a high density and a high, possibly metallic conductivity occurs below the critical temperature $T_c = 1490$ °C. This means that in the case of metals, the phase transition from the liquid to the vapor and the transition of the electronic structure from a metallic liquid to a non-conducting vapor must always be considered together. Special emphasis must be placed on the change in the type of chemical bonding that accompanies the phase transition. Whereas metallic bonding, *i. e.* interaction between ions surrounded by a polarizable degenerate electron gas, is present in the liquid, the forces between the atoms or molecules (*e. g.* K, K_2, Cs, Cs_2, or Hg) in the non-conducting vapor phase are of the "van der Waals" type.

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Above the critical temperature T_c, the homogeneous supercritical phase can be continuously compressed to densities corresponding to those of liquids without phase separation, and the continuous transition from nonmetallic to metallic behavior can thus be achieved. However, as can be seen from the isobars in Figure 1, the unavoidable pressures are relatively high, with values of up to three times the critical pressure of 1510 bars.

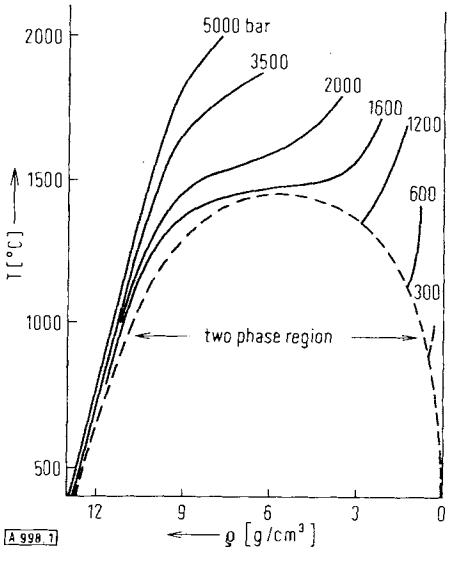


Fig. 1. Equation of state of liquid and gaseous mercury. The broken line shows the liquid-vapor coexistence curve (cf. [8, 9, 13]).

The extremely high temperatures and high pressures are also the reason why little attention was paid to the liquid-vapor phase behavior of metals, and especially to the critical points, until a few years ago, despite the fact that almost 80% of the elements in the periodic system are metals in the solid or liquid states at normal pressure. As can be seen from Table 1, the measured or estimated critical temperatures range from 1490 °C for mercury to 20000 °C for tungsten. The boiling points T_b and the ratios T_c/T_b are also given in the table for comparison. For most nonmetallic substances, such as inert gases or organic liquids, the above ratio is approximately 1.5. The metals deviate from this rule, with values of between 2.1 and 4. Since the critical pressures are also relatively high, the simultaneous use of high temperatures and pressures is always necessary for experiments close to the critical point. The first attempt to determine the critical point of mercury was made by *Bender*[14, 15] in 1915. The densities ρ_V and ρ_L

Table 1. Boiling point at 1 bar, critical temperature, and critical pressure for a number of metals.

Metal	Normal boiling point T_b [K]	Critical temperature T_c [K]	T_c/T_b	Critical pressure p_c [bar]	Ref.
Hg	630	1760	2.54	1510	[8, 9]
Cs	963	2020	2.10	110	[10, 44]
K	1031	2200	2.10	155	[43]
Na	1156	2570 [a]	2.2	350 [a]	[16, 18]
Pb	2016	5400 [a]	2.7	850 [a]	[16]
Sn	2896	8720 [a]	3.0	2100 [a]	[16]
Fe	3148	10000 [a]	3.2	—	[16]
W	5808	23000 [a]	3.9	> 10000 [a]	[16]

[a] Estimated.

of the vapor and of the liquid were measured in fused quartz capillaries under saturation pressure up to 1380 C. It was found that the arithmetic mean of the densities, $0.5\,(\rho_L+\rho_V)$, varies linearly with the temperature in the range covered by the measurements. On the assumption that the linearity is exhibited by all metals up to the critical point, *Grosse*[16, 17] estimated the critical temperatures of many metals from experimental data obtained at low temperatures for the liquid densities and vapor densities of these metals[18]. It was only through the development of a special experimental technique, favored by the rapid advances in the production of high-temperature materials during the past few years, that a number of experiments have been possible on the three metals having the lowest critical temperatures, *i.e.* mercury, cesium, and potassium. The fundamental thermodynamic properties density, vapor pressure, and critical data and the electronic properties electric conductivity, thermoelectric power, Hall effect, and optical absorption have been measured in some cases.

For these investigations, it was necessary to extend the measurements in particular to temperatures of up to 2300 °C and pressures of up to 5000 bars. It is important here to determine *e.g.* the conductivity, the density, or the optical absorption in measuring cells with accurately defined geometries. Materials found to be suitable for such cells are pure tungsten, molybdenum, niobium, the high-temperature alloy tungsten-rhenium, and (only for measurements on mercury) the sintered nonmetals aluminum oxide, thorium oxide, beryllium oxide, and, especially for optical measurements, corundum single crystals. These materials are resistant to the supercritical, compressed metals under investigation. However, cells of this kind cannot be constructed in such a way that they can still withstand a high internal pressure at temperatures of 2000 C. An arrangement was therefore used in which the measuring cells, together with the necessary resistance furnaces, are placed in larger autoclaves, which are filled with pure argon or helium under the same pressure as the fluid metal inside the measuring cell. This avoids any mechanical stress on the tungsten, molybdenum, niobium, or ceramic cells.

2. Investigations on Mercury

The metal that has been most intensively studied is mercury, whose critical temperature is within a range that is experimentally readily accessible. Figure 2 shows the DC electric conductivity (probably the most characteristic metallic property) found by various groups of workers[8, 9, 12, 13, 19, 20] as a function of the pressure for a number of subcritical and supercritical temperatures.

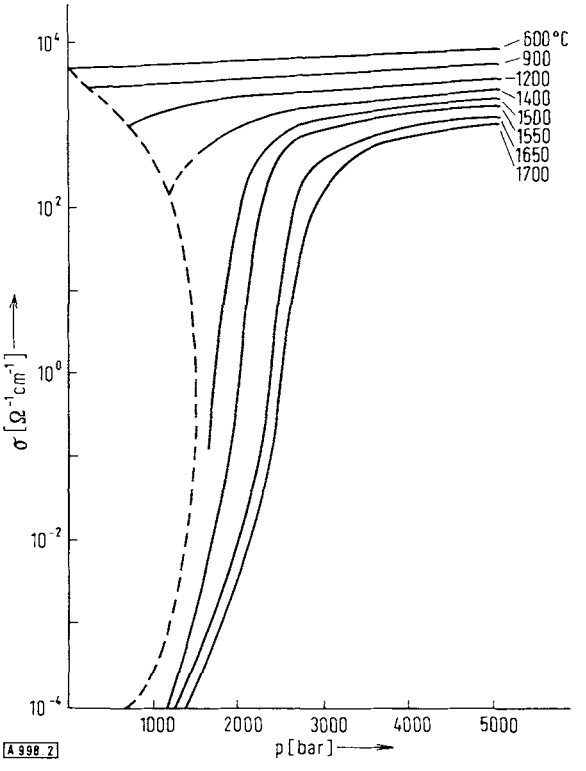


Fig. 2. Specific electric conductivity of mercury at subcritical and supercritical temperatures (in C) as a function of the pressure. The broken line shows the probable course of the conductivity of the coexisting liquid and gaseous phases (cf. [8, 9, 19]).

At subcritical temperatures in the liquid phase, the conductivity σ changes only very slightly with pressure. Thus a pressure increase of 1000 bars at 600 C increases σ by only 6%. A strong dependence on pressure is observed only at supercritical temperatures. A pressure increase of only 500 bars in the vicinity of the critical point can sometimes increase the conductivity by up to five orders of magnitude. This strong pressure dependence, which is also found for the metals cesium[10] and potassium[11], is undoubtedly due to the great decrease in the mean interatomic distance as the pressure is increased in this range. Slightly above the critical point of a pure substance, the compressibility is very high (cf. Fig. 1). An at least partly simple relation is therefore to be expected between the conductivily and the density. This is confirmed by Figure 3, which shows σ as a function of the mean interatomic distance, as measured by the cube root of the reciprocal

number density N[*] of the mercury atoms. The upper scale shows the density in grams per cubic centimeter for comparison.

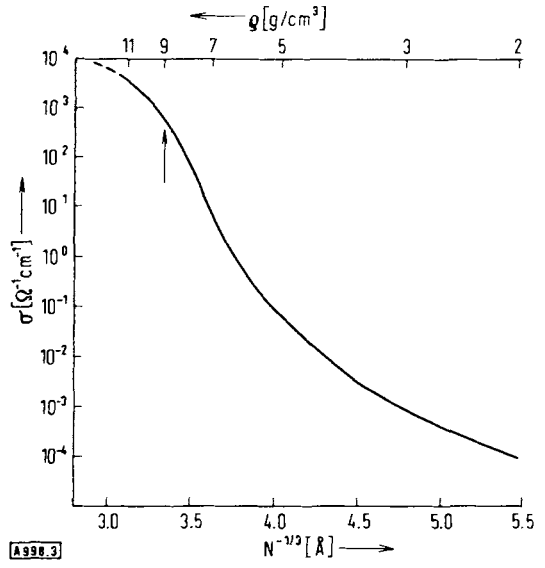


Fig. 3. Specific electric conductivity of mercury at a constant supercritical temperature of 1550 °C as a function of $N^{-1/3}$ (as a function of the density). N = number density of Hg atoms.

Between 3 and 5.5 Å, corresponding to a density change from 13.5 to 2 g/cm^3, the conductivity changes from approximately $10^{+4}\,\Omega^{-1}\,cm^{-1}$, a typical value for metals, to $10^{-4}\,\Omega^{-1}\,cm^{-1}$, a typical value for insulators at high temperatures (*e.g.* quartz: $\approx 10^{-5}\,\Omega^{-1}\,cm^{-1}$ at 1200 °C). This transition from a metallic to a nonmetallic state can best be explained on the basis of the band model[21], which has been known in solid-state chemistry and physics for more than 40 years. The clearest model is the "tight binding approximation"[22], in which a metal is regarded as a collection of atoms that are brought together from an infinite distance apart. Regardless of the arrangement of the atoms, this model fundamentally always leads to the following picture. If the atoms are brought close together by an increase in density, the Coulomb interaction between the atomic cores and the overlapping parts of the atomic orbitals leads to splitting of the energy levels of the entire system and hence to splitting of the levels into energy bands. The energy bands, whose widths depend mainly on overlap of atomic orbitals of nearest neighbors, and hence on the interatomic distance, are derived from the discrete energy levels of the isolated atoms forming the system, and consist of a large number of closely spaced individual levels. A substance is a metal if the states of a band are only partly occupied, or if a fully occupied band overlaps with an empty band having a higher energy. In both cases, there is no forbidden energy zone between the occupied ground states and the empty excited states. Electrons in states close to the highest occupied energy level are thus freely mobile. The second case is found in solid and liquid mercury having high densities (about 13.5 g/cm^3). The 6s band formed from the doubly occupied 6s level of the isolated atom is fully occupied and overlaps sufficiently with the higher 6p band, which forms the conduction band.

The situation to be expected on expansion of a simple, *e.g.* cubic crystal constructed from divalent atoms of this type is shown schematically in Figure 4. It is assumed here that the divalent atoms are arranged in a lattice in which they are all equidistant from one another (interatomic distance a). In an imaginary experiment, this distance can be continuously increased. As a increases, both the occupied valence band α and the unoccupied conduction band β become narrower; *i.e.* the overlap between the two bands is decreased as a result of the expansion, and ultimately, at a distance a_0, an energy gap ΔE is formed between the bands and rapidly increases with increasing a. The expanded crystal is then a semiconductor. An electric current can flow only if electrons pass from the valence band α into the conduction band β as a result of thermal or optical excitation.

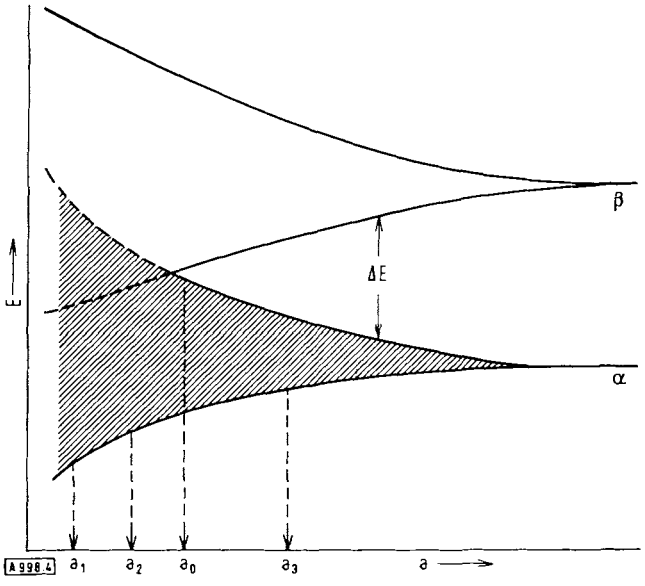


Fig. 4. Schematic representation of the formation of energy bands from the energy levels of the atoms for a divalent solid metal as a function of the interatomic distance a. α = occupied band; β = empty band; ΔE = energy gap.

However, this model cannot be applied to liquid or gaseous systems without substantial modification. In a liquid system or even in a solid at high temperatures with pronounced fluctuations of the density and hence of the interatomic distance, there may not be any sharply bounded forbidden energy zone. The distance variations always lead to a number of allowed energy states within this zone due to the interaction of the electron with the ions in their instantaneous positions. *Mott*[23, 24] has shown that the true energy gap of the crystalline semiconductor is replaced in a noncrystalline system by a minimum in the density of states $N(E)$, which is also called a "pseudogap". The quantity $N(E)\cdot dE$ denotes the number of energy states in the unit volume which is available for an electron with a given spin direction in the energy range between E and $E+dE$. The proposed density of states $N(E)$ for expanded crystalline and liquid mercury is shown schematically in Figure 5 as a function of the energy for various mean interatomic distances a_1, a_2, and a_3 (cf. Fig. 4). In the upper part of the figure, the broken lines indicate the density of states of the separate bands of the solid; the continuous lines show the sum of the two overlapping bands. The lower part of the figure, on the other hand, shows the presumed course of $N(E)$ for liquid mercury. Sharp contours such as are possible in the density of states curve of a solid do not occur

[*] N = number of mercury atoms per cm^3.

here, and the "pseudogap" mentioned above is found in place of the energy gap of the solid. For comparison, the broken line shows the course of the density of states $N(E)_{free}$ calculated for a free degenerate electron gas (formed from the two valence electrons of the mercury atoms). The arrows indicate the most probable position of the Fermi level[*].

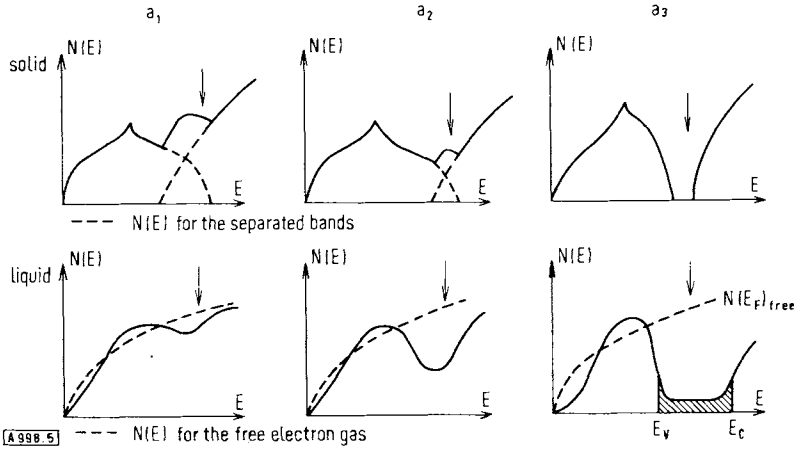


Fig. 5. Schematic representation of the density of the electronic states $N(E)$ in the two bands of Fig. 4 for the three different interatomic distances a_1, a_2, and a_3. The upper part of the figure shows the assumed course of $N(E)$ for a crystal, and the lower part the course for a liquid system. Localized electronic states are indicated by shading. The arrow shows the position of the Fermi energy.

For expanded mercury, the Fermi level, *i.e.* the highest occupied level, is within the "pseudogap". The density of states at the Fermi energy $N(E_F)$ decreases with increasing mean interatomic distance. A particularly interesting case is that shown under a_3. In the discussion of strongly perturbed amorphous or liquid semiconductors, various authors[25-28] have suggested that states may be localized in regions of low density of states. Calculations for a randomly constructed, one-dimensional chain of atoms[24] had shown that unlike in the case of a periodic potential, where waves can travel unhindered through the entire lattice, localized electronic states now occur. This result is applied to three-dimensional systems, for which no exact calculations have been carried out. The idea of such localized states is not new to semiconductor chemists and physicists. Localized donor and acceptor levels arise in crystalline semiconductors as a result of isolated centers of disturbance. The only novelty is the model of a practically continuous distribution of localized states. According to *Mott*[29], there should be exactly defined energies that separate regions with localized states from those with unlocalized states. These energies are indicated in Figure 5 by E_C and E_V (from conduction and valence bands). The region of localized states is shaded. The Fermi energy probably lies in this region in the case of mercury. This model allows the interpretation of the transition from metallic to nonmetallic behavior observed in Figure 3.

However, measurement of the conductivity, which is determined by the nature and concentration of the charge carriers and by their mobility, is not enough for this purpose. Additional measurements of the absolute thermoelectric power and of the Hall effect[*] are necessary for the separate determination of the individual factors. It should be mentioned that the Hall effect can be used only for the metallic region of expanded mercury. The normal theory of the Hall effect for crystalline semiconductors is not valid for liquid or amorphous semiconductors, and no new theory has been produced so far, so that the type or the concentration of the charge carriers cannot be determined from such a measurement.

The findings so far can be interpreted as follows: Between 13.5 and 11 g/cm^3, the course of $N(E)$ is as shown in Figure 5 under a_1. The density of states $N(E_F)$ at the Fermi energy is not very different from the calculated "free density of states" $N(E_F)_{free}$. The conductivity behavior in this region can be explained by the free-electron model. According to this model, the conductivity is σ_{free} and the Hall constant is $R_{H,free}$[30].

$$\sigma_{free} = \frac{e^2 n^{2/3} L}{(3\pi^2)^{1/3}\hbar} \quad (1)$$

$$R_{H,free} = \frac{1}{nec} \quad (2)$$

L is the mean free path of the electrons, n is the electron concentration, and all other symbols have the usual meanings. Figure 6 shows the results obtained by *Even* and *Jortner*[20, 31] for the Hall constant of expanded liquid mercury as a function of the density. The quantity plotted is the ratio of the measured Hall constant R_H and the value calculated for $R_{H,free}$ from eq. (2) on the assumption of two free electrons per atom. No deviation from the "free Hall constant" is observed between 13.5 and 11 g/cm^3. Since the change in n, which is due only to the change in density, is not large, the dependence of the conductivity on the density up to 11 g/cm^3 can only be explained by a decrease in the mean free path. A calculation of the free path of the electrons in mercury as a function

[*] For metals at 0 K, the Fermi level is the highest occupied energy level of the conduction band. For an insulator or an intrinsic semiconductor, the Fermi level lies exactly in the center of the forbidden zone.

[*] When a steady current is flowing in a steady magnetic field electromotive forces are developed which are at right angles both to the magnetic force and to the current and are proportional to the product of the intensity of the current and the magnetic force.

of the density has been carried out by *Evans*[32] on the basis of the Ziman model[33–35] of quasi-free electrons. The resulting volume coefficient for the conductivity $(\partial \ln \sigma / \partial \ln V)_T$ (V = volume), with a value of 6.7 ± 1.0, is in reasonably good agreement with the experimental value of 8.0[1,2]. The differences between the experimental values and those calculated from the free-electron model become distinctly greater for densities of less than 11 g/cm³. At 11 g/cm³, however, the conductivity is already so low that this model can no longer allow a good description. The mean free path of the electrons, formally calculated from eq. (1), is now comparable with the mean distance a between the ions, and the Hall constant begins to deviate considerably from $R_{H,free}$; it increases very rapidly with decreasing density (Fig. 6).

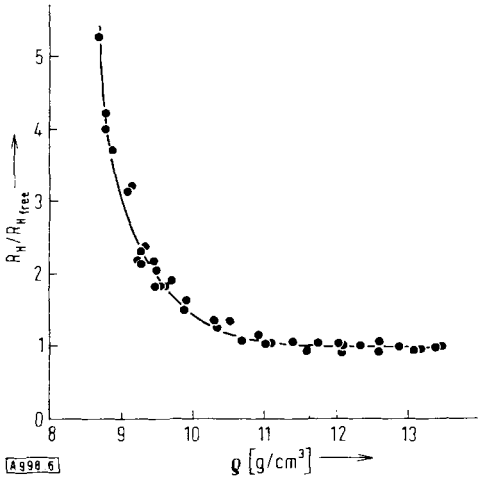


Fig. 6. Ratio of the measured Hall constant R_H and the Hall constant $R_{H,free}$ calculated for a free degenerate electron gas from eq. (2) for liquid mercury as a function of the density of the mercury (cf. [20, 31]).

This suggests that for densities lower than 11 g/cm³, the density of states at the Fermi energy $N(E_F)$ deviates strongly from $N(E_F)_{free}$, *i.e.* that the case is as indicated under a_2 in Figure 5. *Mott*[23,30] and *Friedman*[36] found that σ and R_H then depend on $N(E_F)$.

$$\sigma = \sigma_{free} \times \left(\frac{N(E_F)}{N(E_F)_{free}} \right)^2 \tag{3}$$

$$R_H = R_{H,free} \Big/ \left(\frac{N(E_F)}{N(E_F)_{free}} \right) \tag{4}$$

In the calculation of σ_{free}, L is taken to be equal to the mean interatomic distance a. Eqs. (3) and (4) allow independent calculations of $N(E_F)/N(E_F)_{free}$. The values obtained from the two measured quantities agree perfectly, and are plotted in Figure 7 as a function of the density. $N(E_F)$ decreases very rapidly with the density, and at 9 g/cm³, it is only about 30% of the value for the free electron $N(E_F)_{free}$.

For densities lower than 9 g/cm³, *i.e.* $N(E_F)/N(E_F)_{free} < 0.3$, σ and R_H can no longer be described by eqs. (3) and (4)[31]. Moreover, the dependence of the conductivity on temperature and density shows a pronounced increase with decreasing density in this range. Figure 8 shows the measured volume coefficients $(\partial \ln \sigma / \partial \ln V)_T$ and temperature coefficients $(\partial \ln \sigma / \partial \ln T)_V$[9,12] as functions of the density.

The temperature dependence of the conductivity is always high and positive when the current is produced by thermally

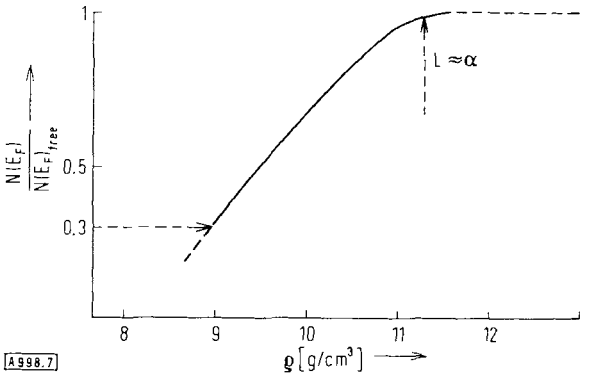


Fig. 7. Density of states at the Fermi energy $N(E_F)$ as calculated from eqs. (4) and (5) for mercury as a function of the density of the mercury. $N(E_F)_{free}$ is the density of states calculated for the free electron gas [21, 22].

activated charge carriers, as *e.g.* in a conventional solid semiconductor, in which the valence and conduction bands are separated by an energy gap. However, by optical absorption measurements[37,38] on compressed gaseous mercury, it has been shown that the 6s and 6p bands in mercury overlap for densities greater than 5 g/cm³, so that there is no true energy gap between the two bands; the density of states at the Fermi energy $N(E_F)$ is finite. It is therefore probable

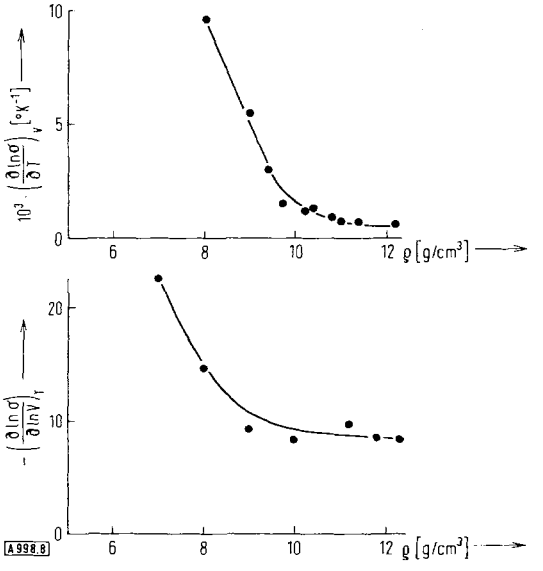


Fig. 8. Temperature and volume coefficients of the specific conductivity σ for liquid mercury as a function of the density of the mercury (cf. [9,12,42]).

that the case indicated in Figure 5 under a_3 is now present. The states in the vicinity of E_F are localized. An electric current can flow only if excitation causes electrons to pass from states close to E_F into mobile states above E_C. The conductivity (and this is in agreement with experiment, Fig. 8) must therefore be strongly dependent on the temperature. The following relation is expected for a constant density:

$$\sigma = \sigma_0 \times \exp - \left(\frac{E_C - E_F}{kT} \right) \tag{5}$$

In eq. (5), $(E_C - E_F)$ should increase with decreasing density; this also corresponds to the pronounced increase in the measured volume coefficients for densities lower than 9 g/cm³.

The validity of eq. (5) unfortunately cannot be checked by conductivity measurements alone, since the shape of the density of states curve $N(E)$, the region of localized states, and hence $(E_C - E_F)$ itself depend on the temperature. Several research groups have therefore investigated the absolute thermoelectric power of liquid and gaseous mercury as a function of pressure and temperature[12, 39-41].

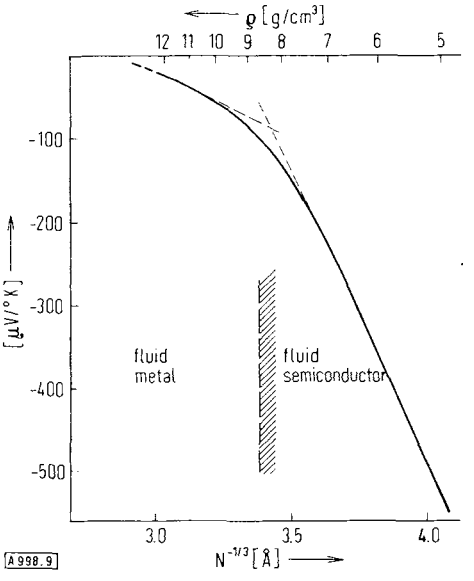


Fig. 9. Absolute thermoelectric power of mercury at a constant supercritical temperature of 1550 °C as a function of $N^{-1/3}$ (as a function of the density).

The experimental data are shown in Figure 9 as a function of the cube root of the reciprocal number density N of the mercury atoms and as a function of the density. Between 13.5 and 9 g/cm³ one finds values of between -5 and $-90\,\mu V/°K$, which are typical of solid and liquid metals. For densities lower than 9 g/cm³, the absolute value of the thermoelectric power very rapidly increases, and finally reaches $550\,\mu V/°K$ at 5 g/cm³; absolute thermoelectric powers as high as this are observed in semiconductors. If, as has been assumed so far, the current in mercury at densities lower than 9 g/cm³, as in a conventional semiconductor, is mainly due to thermally excited electrons[42], the thermoelectric power is given by[12, 30]

$$S = \frac{k}{e} \times \left(\frac{E_C - E_F}{kT} + \text{const.} \right) \qquad (6)$$

k = Boltzmann's constant

Combination of eqs. (5) and (6) gives an experimentally checkable relation between the conductivity σ and the absolute thermoelectric power S[12, 30].

$$\ln \sigma = \frac{eS}{k} + \text{const.} \qquad (7)$$

This relation (7) is found in Figure 10 to be confirmed for mercury densities lower than 8 g/cm³.

The measured slope of the straight line, *i.e.* $1.2 \times 10^{+4}$ (°K/V), agrees satisfactorily with the calculated value of $e/k = 1.16 \times 10^{+4}$ (°K/V). The transition from the liquid or gaseous metal to the liquid or gaseous semiconductor thus seems to occur in the density range between 8 and 9 g/cm³ in the case of mercury. It should be emphasized that this

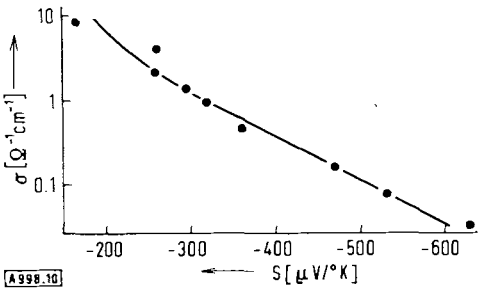


Fig. 10. A plot of the logarithm of the conductivity σ as a function of the thermoelectric power S of expanded liquid mercury gives a straight line with a slope of $1.2 \times 10^{+4}$ [°K/V] for densities lower than 8 g/cm³ (cf. eq. (7)).

transition does not occur at the critical point of mercury. The critical density of 5.3 g/cm³ is much lower. Moreover, liquid mercury expanded to a density of less than 9 g/cm³ then exhibits semiconducting properties instead of metallic properties.

3. Investigations on Alkali Metals

There are far fewer experimental results available for the univalent alkali metals, which have the lowest critical temperatures after mercury. The high chemical reactivity of these metals, particularly the violence of the reactions with nearly all available electrically insulating materials at high temperatures, presents great difficulties. Only the vapor pressure curve, the critical data, and the electric conductivity have been measured for potassium[11, 43], and the vapor pressure curve[10, 44, 45], the densities[46, 47], the critical data[11, 46], the conductivity[10, 48, 49], and the thermoelectric power[49] for cesium. Figure 11a shows conductivity isotherms for potassium at subcritical and supercritical temperatures as functions of the pressure. The behavior observed is qualitatively the same as for the divalent mercury. The pressure dependence is relatively low at subcritical temperatures. Only at temperatures above the critical point does one observe a steady but steep decrease in the conductivity with decreasing pressure, which indicates the transition to nonmetallic behavior. However, one difference from the behavior of mercury should be pointed out. At the critical point, which is the end point of the vapor pressure curve shown in Figure 11b ($p_c = 155$ bars, $T_c = 1925$ °C), a conductivity of $\sigma = 10$ to $100\,\Omega^{-1}\,cm^{-1}$ is recorded. This is relatively high in comparison with the value of only 10^{-1} to $10^{-2}\,\Omega^{-1}\,cm^{-1}$ measured at the critical point of mercury.

By combination of conductivity and density data for cesium, a discussion of the conductivity behavior as a function of the interatomic distance is again possible. Figure 12 shows the conductivity σ at the constant supercritical temperature of 2000 °C as a function of the cube root of the reciprocal number density N of the cesium atoms. Between $N^{-1/3} = 3 \times 10^{-7}$ and 10^{-7} cm, the conductivity increases only slightly with decreasing interatomic distance, whereas in the relatively narrow range between 10^{-7} and 0.5×10^{-7} cm, it increases by three orders of magnitude to values that are typical of liquid metals (for comparison, the conductivity of liquid cesium at 60 °C and 1 bar is $2.4 \times 10^{+4}\,\Omega^{-1}\,cm^{-1}$). In the first case, the region of large interatomic distances, σ is of the order of $1\,\Omega^{-1}\,cm^{-1}$, and is certainly nonmetallic.

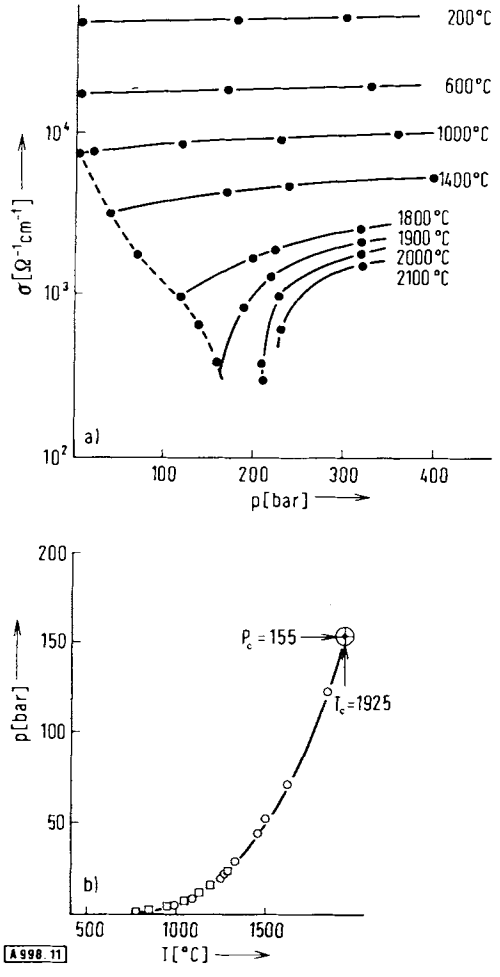


Fig. 11. a) Specific electric conductivity σ at subcritical and supercritical temperatures as a function of the pressure. b) Vapor pressure curve up to the critical point of potassium. The broken line shows the probable conductivity of liquid potassium at the saturation pressure (cf. [11, 43]).

In this range we probably have a dense gas of Cs atoms and Cs_2 molecules, and the conductivity is caused by thermal ionization of the neutral particles. Calculation of σ with the simple Saha equation for the degree of ionization[50] and the Chapman-Enskog theory[51] for charge transport in dilute gases gives a conductivity of $0.7\,\Omega^{-1}\,cm^{-1}$ for $N^{-1/3}=10^{-7}$ cm, in good agreement with experiment. The degree of ionization calculated from the ionization potential of the isolated atom is $\alpha=1.5\times10^{-4}$, and $40\,Å^2$ [52] is used as the mean collision cross section of the neutral cesium atom.

With decreasing distance, the conductivity increases by a factor of about 2 down to 1.5×10^{-7} cm; the only explanation for this is an increase in the thermal ionization. This is probably due to the increasing content of more complex molecular aggregates in the cesium gas with decreasing distance, *i.e.* with increasing pressure. For $N^{-1/3}=1.5\times10^{-7}$ cm, the estimated dimer content based on the molecular data for Cs_2 from spectroscopic measurements[53] is 10%. No accurate measurements of the ionization potential of Cs_2 are known. However, measurements on small clusters of sodium atoms show that there has already been a considerable decrease in the ionization potential[54]. If a similar effect existed for cesium clusters, this would lead to an increase in the degree of ionization, and hence to an increase in the conductivity.

The transition from the thermally activated conductivity of the dilute gas to the metallic conductivity of the compressed gas occurs at interatomic distances $N^{-1/3}$ of less than 10^{-7} cm. This transition cannot be predicted from the usual one-electron approximation of solid-state physics, the band model described in Section 2. According to this model, in a crystalline material consisting of univalent atoms, there is always a half-filled conduction band, whatever the distance between the atoms.

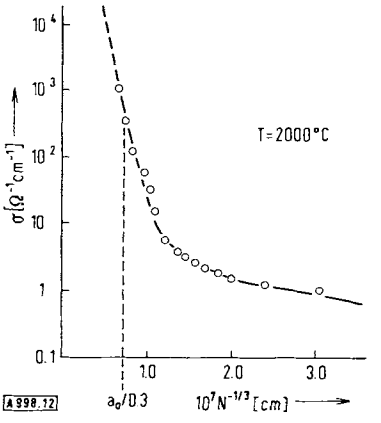


Fig. 12. Specific electric conductivity of cesium at a constant supercritical temperature of 2000 °C as a function of $N^{-1/3}$. N = number density of the Cs atoms, $a_0=2.33$ Å (radius of the neutral Cs atom [55]; cf. [10, 35, 47, 48]).

As was first pointed out by *Mott*[56,57], however, this prediction of the model is wrong, since the Coulomb interaction between the electrons cannot be disregarded at large interatomic distances. *Mott*[56–58], *Kohn*[59], and *Hubbard*[60,61] have carried out theoretical treatments of this electron-electron interaction for crystalline univalent substances. Though their models differ in detail from one another, they all predict nonmetallic behavior for large interatomic distances and metallic behavior for small interatomic distances. The first rough estimate of the critical interatomic distance at which the transition should occur was made by *Mott*. This author found that the activation energy required for the production of charge carriers at large distances tends discontinuously toward zero if the interatomic distance $N^{-1/3}$ and the radius of the neutral atom a_0 are related as follows:

$$N^{-1/3}a_0 \geq 0.3 \qquad (8)$$

The critical value of $N^{-1/3}$ calculated from eq. (8) for the transition from metallic to nonmetallic behavior is in fact situated in the region of the rapid increase in conductivity (Fig. 12). An accurate analysis of the temperature dependence of the conductivity of cesium shows, however, that the change from a negative temperature dependence of the conductivity (typical of liquid univalent metals[62]) to a positive temperature dependence occurs at a distinctly lower interatomic distance than that calculated from eq. (8). Table 2 shows the mean interatomic distance $N^{-1/3}$, the mean free path L of the electrons, and the temperature coefficient $(\partial\ln\sigma/\partial\ln T)_V$ of the conductivity as functions of the density. The change in the sign of $(\partial\ln\sigma/\partial\ln T)_V$ occurs at a density at which $N^{-1/3}=5.9\,Å\approx L$. This is distinctly smaller than the value of 7.8 Å found for $N^{-1/3}$ from eq. (8).

There is at present no satisfactory theory for the metal-nonmetal transition in liquid or gaseous expanded univalent metals,

Table 2. Mean interatomic distance $N^{-1/3}$, mean free path of the electrons L (formally calculated from eq. (1)), and temperature coefficient of the conductivity at constant volume $(\partial \ln \sigma / \partial \ln T)_V$ for cesium as a function of the density ρ. The mean temperature is 1750 °C.

ρ [g/cm³]	$N^{-1/3}$ [Å]	L [Å]	$\left(\frac{\partial \ln \sigma}{\partial \ln T}\right)_V$
1.5	5.16	15.5	− 1.2
1.3	5.41	12.5	− 0.9
1.1	5.72	9.8	− 0.4
0.9	6.11	6.1	+ 1.2
0.7	6.65	2.0	+ 10.4
0.5	7.44	0.5	+ 54.0

which should take into account the effects of thermal motion and of thermal density fluctuations.

4. Outlook

It seems important to point out that despite the considerable number of experimental facts that have been described in this report, the chemical or physical mechanism underlying the metal-nonmetal transition is still largely unknown. Nevertheless, the findings show that, however one may describe the interatomic forces in a liquid metal, the description must change with the density. As the atoms move farther apart on expansion, the metallic bonding changes into nonmetallic bonding. Recent measurements on the viscosity[63] of expanded liquid and gaseous mercury may possibly provide information about the nature of the interatomic forces.

A second unsolved problem is the formation of the "pseudogap" and the occurrence of localized states within this gap. Optical absorption and emission measurements and photoconductivity measurements are expected to yield information about the pseudogap. The part played in the formation of the localized states by the development of large molecular aggregates, which can decisively influence the transport of electrons, is one of the most pressing theoretical questions. Another question that must be examined in this connection is whether a univalent metal (*e.g.* Cs or K) is really univalent in the gaseous state at low densities. Diatomic molecules (Cs_2 and K_2) have a bond energy of more than 10 kcal/mol, so that for the gaseous alkali metals, the metal-nonmetal transition could be initiated by overlap of energy bands of the diatomic molecule. It should be possible to check this hypothesis by magnetic susceptibility measurements.

Very many problems are thus still awaiting clarification. The experiments are difficult and time-consuming, but the result could be a deeper understanding of the metal-nonmetal transition in general. The great similarity between the observations on compressed metal vapors and those on metal-ammonia solutions, solutions of metals in salts, and liquid mixtures *e.g.* of magnesium with bismuth or of thallium with tellurium, in which a transition from metallic to nonmetallic behavior occurs in the vicinity of the composition Mg_3Bi_2 or Tl_2Te[64], suggests that a single theory might be capable of describing all these very different systems.

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[1] *W. Weyl*, Ann. Phys. (Leipzig) *197*, 601 (1863).

[2] *C. A. Kraus*, J. Chem. Educ. *30*, 83 (1953).

[3] *U. Schindewolf*, Angew. Chem. *80*, 165 (1968); Angew. Chem. internat. Edit. *7*, 190 (1968).

[4] *H. R. Bronstein* and *M. I. Bredig*, J. Amer. Chem. Soc. *80*, 2077 (1958); J. Phys. Chem. *65*, 1220 (1961).

[5] *T. C. Waddington*: Non-Aqueous Solvent Systems. Academic Press, New York 1965.

[6] *H. Fritzsche*, J. Phys. Chem. Solids *6*, 69 (1958).

[7] *F. Birch*, Phys. Rev. *41*, 641 (1932).

[8] *F. Hensel* and *E. U. Franck*, Ber. Bunsenges. Phys. Chem. *70*, 1154 (1966).

[9] *I. K. Kikoin* and *A. R. Sechenkov*, Phys. Metals Metallogr. *24*, 5 (1967).

[10] *H. Renkert*, *F. Hensel*, and *E. U. Franck*, Ber. Bunsenges. Phys. Chem. *75*, 507 (1971).

[11] *W. F. Freyland* and *F. Hensel*, Ber. Bunsenges. Phys. Chem. *76*, 347 (1972).

[12] *R. W. Schmutzler* and *F. Hensel*, Ber. Bunsenges. Phys. Chem. *76*, 531 (1972).

[13] *D. R. Postill*, *R. G. Ross*, and *N. E. Cusack*, Advan. Phys. *16*, 493 (1967).

[14] *J. Bender*, Phys. Z. *16*, 246 (1915).

[15] *J. Bender*, Phys. Z. *19*, 410 (1918).

[16] *A. V. Grosse*, J. Inorg. Nucl. Chem. *22*, 23 (1961).

[17] *A. V. Grosse*, Rev. Hautes Temp. Refract. *3*, 115 (1966).

[18] *I. G. Dillon*, *P. A. Nelson*, and *B. S. Swanson*, J. Chem. Phys. *44*, 4229 (1966).

[19] *R. W. Schmutzler*, *F. Hensel*, and *E. U. Franck*, Ber. Bunsenges. Phys. Chem. *72*, 1194 (1968).

[20] *U. Even* and *J. Jortner*, Phys. Rev. Lett. *28*, 31 (1972).

[21] *N. F. Mott* and *H. Jones*: The Theory of the Properties of Metals and Alloys. Clarendon Press, Oxford 1936.

[22] *J. M. Ziman*: Principles of The Theory of Solids. Cambridge University Press, Cambridge 1964, p. 83.

[23] *N. F. Mott*, Phil. Mag. *13*, 989 (1966).

[24] *N. F. Mott*, Advan. Phys. *16*, 49 (1967).

[25] *H. Fröhlich*, Proc. Roy. Soc. London *A 188*, 521 (1947).

[26] *N. F. Mott*, Phil. Mag. *17*, 1259 (1968).

[27] *M. H. Cohen*, J. Non-Cryst. Solids *2*, 432 (1970).

[28] *A. I. Gubanov*: Quantum Electron Theory of Amorphous Semiconductors. Consultants Bureau, New York 1965.

[29] *N. F. Mott*, Phil. Mag. *19*, 835 (1969).

[30] *N. F. Mott* and *E. A. Davis*: Electronic Processes in Non-crystalline Materials. Clarendon Press, Oxford 1971.

[31] *U. Even* and *J. Jortner*, Phil. Mag. *25*, 715 (1972).

[32] *R. Evans*, J. Phys. *C*, Metal Phys. Suppl. *2*, 137 (1970).

[33] *J. M. Ziman*, Phil. Mag. *6*, 1013 (1961).

[34] *C. C. Bradley*, *T. E. Faber*, *E. G. Wilson*, and *J. M. Ziman*, Phil. Mag. *7*, 865 (1962).

[35] *T. E. Faber*: An Introduction to the Theory of Liquid Metals. Cambridge University Press, Cambridge 1972.

[36] *L. Friedman*, J. Non-Cryst. Solids *6*, 329 (1971).

[37] *F. Hensel*, Phys. Lett. *31 A*, 88 (1970).

[38] *F. Hensel*, Ber. Bunsenges. Phys. Chem. *75*, 847 (1971).

[39] *R. W. Schmutzler* and *F. Hensel*, Phys. Lett. *35 A*, 55 (1971).

[40] *L. J. Duckers* and *R. G. Ross*, Phys. Lett. *38 A*, 291 (1972).

[41] *V. A. Alekseev*, *A. A. Vedenov*, *Yu. F. Rizkov*, *V. G. Ovtsharenko*, and *A. N. Starostin*, First Soviet Conf. Metal Dielectric Transition, Moscow, USSR, June 21–23, 1972.

[42] *R. W. Schmutzler* and *F. Hensel*, J. Non-Cryst. Solids *8*, 718 (1972).

[43] *W. F. Freyland* and *F. Hensel*, Ber. Bunsenges. Phys. Chem. *76*, 16 (1972).

[44] *I. L. Silver* and *C. F. Bonilla*, Fifth Symp. Thermophysical Properties, Amer. Soc. Mech. Engrs., New York 1970, 461.

[45] *J. P. Stone*, *C. T. Ewing*, *J. R. Spann*, *E. W. Steinkuller*, *D. D. Williams*, and *R. R. Miller*, J. Chem. Eng. Data *11*, 315 (1966).

[46] *G. F. Oster* and *C. F. Bonilla*, Fifth Symp. Thermophysical Properties, Amer. Soc. Mech. Engrs., New York 1970, 468.

[47] *V. A. Alekseev*, *V. G. Ovcharenko*, *Yu. F. Ryzhkov*, and *A. P. Senchenkov*, Zh. Eksp. Teor. Fiz. Pisma Red. *12*, 306 (1970).

[48] *H. Renkert*, *F. Hensel*, and *E. U. Franck*, Phys. Lett. *30 A*, 494 (1969).

[49] *H. P. Pfeifer*, *W. F. Freyland*, and *F. Hensel*, Phys. Lett. *43 A*, 111 (1973).

[50] *S. C. Lin*, *E. L. Resler*, and *A. Kantrowitz*, J. Appl. Phys. *26*, 95 (1955).

[51] *S. Chapman* and *T. G. Cowling*: The Mathematical Theory of Non-Uniform Gases. Cambridge University Press, Cambridge 1960.

[52] *R. A. Coombe*: Magnetohydrodynamic Generation of Electrical Power. Chapman & Hall, London 1964.

[53] *G. Herzberg*: Spectra of Diatomic Molecules. Van Nostrand, New York 1950.

[54] *E. J. Robbins, R. E. Leckenby*, and *P. Willis*, Advan. Phys. *16*, 739 (1967).

[55] *J. T. Waber* and *D. T. Cromer*, J. Chem. Phys. *42*, 4116 (1965).

[56] *N. F. Mott*, Proc. Phys. Soc. London *A 62*, 416 (1949).

[57] *N. F. Mott*, Phil. Mag. *6*, 287 (1961).

[58] *N. F. Mott*, Rev. Mod. Phys. *40*, 677 (1968).

[59] *W. Kohn*, Phys. Rev. *A 133*, 171 (1964).

[60] *J. Hubbard*, Proc. Roy. Soc. London *A 276*, 238 (1963).

[61] *J. Hubbard*, Proc. Roy. Soc. London *A 281*, 401 (1964).

[62] *H. P. Pfeifer*, Diplomarbeit, Universität Karlsruhe 1973.

[63] *H. v. Tippelskirch*, Dissertation, Universität Karlsruhe 1973.

[64] *J. E. Enderby* and *E. W. Collings*, J. Non-Cryst. Solids *4*, 161 (1970).

X-Ray Absorption Spectroscopy on Free Molecules

By W. H. Eugen Schwarz[*]

The most recent spectroscopic method that can be applied to chemical problems is X-ray absorption spectroscopy, in which the excitation of individual core electrons of an atom is studied. The analysis of the spectra with the aid of simple theoretical models yields information both about the core orbitals of the atom and about the unoccupied molecular orbitals, from which various molecular properties can be deduced. These not only include charge distribution, electronic configuration, geometry, and spatial and energy characteristics of orbitals of the molecule under investigation; one can also obtain parameters of radicals (such as stability, bond length, ionization potential, and electronic excitation energy) that differ from the molecule under investigation in that the nuclear charge of one atom is one unit higher.

1. Introduction

An important contribution to scientific progress in chemistry is being made by advances in physical and especially spectroscopic methods. The most recent of the spectroscopic methods that is starting to acquire importance in chemistry is X-ray absorption spectroscopy. This term will be applied to spectroscopy in the energy range that leads to optical excitation of "core electrons". This calls for light quanta with an energy of more than 30—50 eV[**], corresponding to wavelengths λ of less than 400—200 Å. This radiation is known as soft X-rays or XUV.

The discovery that the chemical environment influences the X-ray absorption spectrum of a bonded atom was made in 1920 in the laboratory of *Siegbahn sr.* during the investigation of solids[1]. X-ray absorption spectroscopy was first applied to free molecules during the 1930's[2]. The number of publications, mainly dealing with studies on complex compounds[3], has increased since 1945, but it was only during the last few years that the sensitivity and the resolving power of the spectrometers were increased to such a degree that the line spectra that are now obtainable can be effectively used for more detailed chemical problems. The course of the development was similar to that of X-ray photoelectron spectroscopy (ESCA)[4], which has a history extending back over more than 50 years, but which has only recently become a versatile method for use in chemistry as a result of a spectacular breakthrough. The reason why the underlying ideas took so long to reach maturity lay in experimental difficulties, which were overcome in the case of the ESCA method through the development work of *Siegbahn jr.*

A number of experimental questions of X-ray absorption spectroscopy will first be briefly discussed in Section 2. The principles of X-ray absorption spectra and models for their interpretation are presented in Section 3. In the next section, some specific chemical and physicochemical problems will be discussed with the aid of representative spectra.

2. Experimental[9]

Like any other spectrometer, an X-ray absorption spectrometer consists of four parts: a radiation source; a monochromator; an absorption cell; and a detector.

2.1. Radiation Source

One of the main difficulties of X-ray absorption spectroscopy lies in the light sources. Until recently, the radiation used was mainly the bremsstrahlung from *X-ray tubes*[5–7]. However, the intensity of the soft and ultrasoft component in the wavelength range from a few Å to a few hundred Å is low; furthermore, the radiation is strongly divergent. Through the development of special X-ray tubes, it has been possible to extend the range of the useful radiation down to quantum energies of 50 eV ($\lambda \approx 250$ Å), with an energy resolution of at best a few tenths of an eV. The work of a Leningrad research group deserves special mention in this connection[8].

An important breakthrough was achieved with the aid of synchrotron radiation[9–11]. In a *synchrotron* or storage ring,

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[**] 1 eV (electron volt) corresponds to 23 kcal/mol.

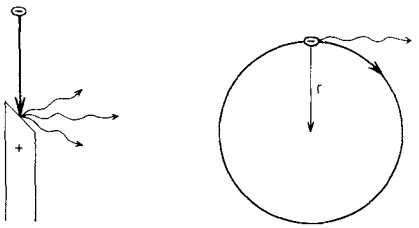


Fig. 1a. X-ray tube (left) and synchrotron (right) as radiation sources (schematic). r = radius vector. ⊖ = electron.

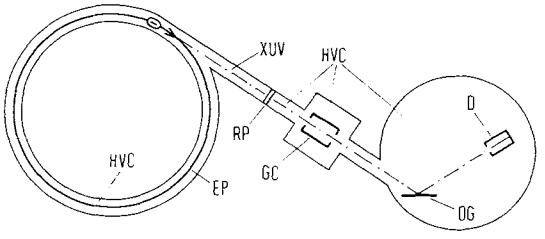


Fig. 1b. Synchrotron radiation absorption spectrometer. DG = diffraction grating, D = detector, EP = circular path of the electrons in the synchrotron, GC = gas absorption cell, HVC = high vacuum channel and vessel, RP = reference probe for measurement of the primary intensity of the radiation, XUV = X-rays.

electrons orbit with almost the velocity of light in a circular path EP (see Fig. 1a and 1b). As a result of the centripetal acceleration, the electrons emit continuous electromagnetic radiation normal to the radius vector r; because of the relativistic velocity of the electrons, the radiation is emitted into a very small solid angle in the forward direction. The high-intensity range of the substantially parallel radiation extends over the entire energy scale in which we are interested. However, the construction and operation of this type of equipment is extremely expensive, partly because of the necessary ultra-high vacuum, so that this radiation can only be used where it occurs, so to speak, as a waste product of high-energy physics or where disused electron accelerators are available. The existing possibilities have so far been used mainly in connection with problems of solid-state physics, whereas there have been relatively few studies on molecules and atoms in the gaseous phase. The latter have been carried out mainly in the installations at Hamburg (DESY), Stoughton (University of Wisconsin), Washington (NBS), and Tokyo.

2.2. Monochromator

Crystal spectrographs, and especially double-crystal spectrographs, are often used as monochromators for medium-soft X-rays ($E > 500\,eV$)[15]. By the use of special organic crystals with large interplanar distances, it has been possible to extend the range of these instruments down to $\lambda = 100\,Å$ ($E \approx 125\,eV$)[19]. *Line gratings* can be used over the entire range of wavelength that are of interest here, especially in the region of the longer-wave ultrasoft X-rays. However, the reflectivities of all materials are so low that it is necessary to use a glancing angle of incidence.

2.3. Absorption Cell

At a gas pressure in the torr range, it is customary to use absorption cells a few cm long with *open entry and exit slits* for the radiation. To maintain the high vacuum in the apparatus, the gas emerging through the slit must be continuously pumped out and replaced by further material flowing into the cell. To overcome this disadvantage, the windows of the cell may be sealed with thin films, *e.g.* of carbon, but one must then be prepared to accept the absorption of the *window films*.

2.4. Detector

The spectra can be recorded on *photographic plates* or, if the intensity of the radiation is sufficiently high, with electronic detectors, particularly open *photomultipliers*. Apart from the improvement of the light sources, it was especially the detector technique that helped to improve the resolution of the instruments, which has been increased to $1 : 10^{-4}$.

The development of the equipment is still proceeding rapidly. Further details and a description of individual instruments can be found in the literature cited.

3. Theoretical Principles

3.1. X-Ray Absorption Spectroscopy in Comparison with Other Spectroscopic Methods

Let us consider a simple molecule (see Fig. 2). The molecular orbitals (MOs) describing the state of the electrons in the molecule can be divided into three classes: 1. *core orbitals*; these are localized close to the nucleus of an atom and describe very strongly bound electrons that are hardly affected by molecule formation; 2. occupied *valence orbitals*; these MOs are derived from the atomic orbitals (AOs) of the valence electron shells, and extend over the entire molecule or at least over several atoms; 3. *virtual MOs*, which are unoccupied in the ground state of the molecule, but can be used for the description of excited electrons.

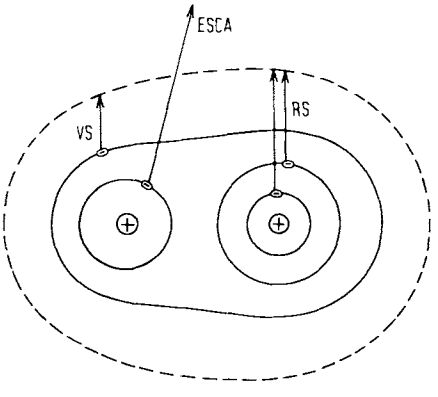


Fig. 2. One-electron excitations in a diatomic molecule on light absorption (VS), X-ray absorption (RS), and ESCA. — — — occupied orbitals, - - - - virtual orbital.

In conventional *absorption spectroscopy with visible and ultraviolet light*, electrons are promoted from the occupied valence MOs into the unoccupied MOs, whereas the more strongly bound core electrons can only be promoted with X-rays, which have much higher energies. Transitions to the virtual MOs are investigated by *X-ray absorption spectroscopy*, and transitions to the continuum by *ESCA* (see Fig. 2). The three methods can therefore compete with and also complement one another.

Since the core MOs are localized on individual atoms and their energy shift essentially depends only on the mean strength of the field of the directly bonded neighboring atoms, X-ray absorption spectroscopy and ESCA are probes for *individual atoms in the molecule*. It should be noted that a higher resolution can generally be achieved in X-ray absorption spectroscopy (0.1—0.01 eV) than in ESCA (1—0.1 eV). In particular, the absolute accuracy of X-ray absorption spectroscopy is usually better, since contact potentials, space charges, and the Fermi level cause displacements of the ESCA values that are difficult to estimate[4]. Moreover, the X-ray absorption spectrum yields information about a whole *series of unoccupied MOs* below (and sometimes also above) the ionization limit, and hence also about the overall structure of the molecule, whereas ESCA gives only the ionization potential *(IP)* of the excited core electron itself. However, ESCA is thus an important complement to X-ray absorption spectroscopy, since knowledge of the ionization potential greatly facilitates the assignment of the X-ray absorption lines corresponding to the unoccupied MOs, which can present considerable difficulties even for molecules of medium size.

Nevertheless, the X-ray absorption spectra are much clearer than the valence electron absorption spectra. There are two reasons for this. Firstly, in the valence electron absorption spectra, the electrons are excited from several valence MOs lying close together, so that several series of lines overlap and interfere with one another. The energies of the core levels, on the other hand, are generally so far apart that two series of lines for different starting levels do not overlap in the X-ray absorption spectrum. Secondly, the interaction of the low-lying hole state (produced by the X-ray excitation) with the excited electron is relatively small, and can be disregarded or taken into account easily by perturbation theory, whereas in the valence electron spectrum, the electron interaction has an extremely strong influence. The *interpretation* of X-ray absorption spectra is therefore much easier, and can often be achieved purely with the aid of simple models, without long quantum-chemical calculations.

The disadvantages of X-ray absorption spectroscopy in comparison with valence electron absorption spectroscopy should not be overlooked. Because of the high excitation energy in X-ray absorption, the absolute energy resolution for the same relative resolution is 1—2 orders of magnitude poorer in the X-ray absorption spectrum than in the valence electron spectrum. The resolving power is also limited by the natural line width, which is frequently 0.1 eV or more owing to the finite lifetime of the highly excited states. Thus in the X-ray absorption spectrum, the vibrational structure can usually be resolved only in the case of small molecules. Finally, the cost of equipment of X-ray absorption spectroscopy is very high, whereas commercial instruments are available for valence electron spectroscopy and ESCA.

3.2. Interpretation Models for X-Ray Absorption Spectra

To be able to use X-ray absorption spectra of molecules for chemical problems, it should be possible to analyze the recorded spectra with the aid of simple qualitative and semi-quantitative principles and without extensive calculations. The models that are important in this connection will now be briefly described.

As was mentioned earlier, the interaction between the electron hole in the atomic core and the excited electron is generally very small, so that to a first approximation the *one-electron model* is sufficient for the interpretation of spectra, *i.e.* the electronic transition energies $h\nu_{ij}$ correspond very closely to the differences in a homogeneous set of one-electron orbital energies ε_i (see Fig. 3):

$$h\nu_{ij} = \varepsilon_j - \varepsilon_i \qquad (1)$$

Simple *MO ideas* about the virtual MOs that form the final levels of the one-electron excitations yield the first indications of the energy and intensity of the absorption bands to be expected. Semiempirical or *ab-initio MO-SCF calculations* must be carried out in more complicated cases.

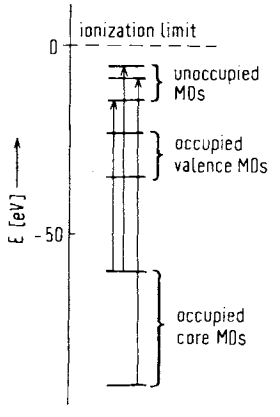


Fig. 3. Electronic excitation by X-ray absorption in the one-electron model.

The virtual MOs can be roughly divided into two classes: 1. MOs derived from the valence electron shells of the atoms, which frequently have antibonding character; 2. MOs lying outside the valence electron shells, so-called Rydberg orbitals with nonbonding character. The valence electron spectra, as indicated above, cannot generally be interpreted in the one-electron MO model. Because of the great distance between the Rydberg MOs and the valence electron shell, however, this can be achieved quite satisfactorily for the optical Rydberg spectra. There is therefore a close *correlation between the Rydberg spectra* of related molecules in the normal optical and X-ray ranges, which can be used for interpretation purposes. In CO, for example, if a 1s electron of carbon is excited, the positive C nucleus will be shielded by only a single 1s electron instead of by two. The effect is the same, to a first approximation, whether a core electron is removed or the nuclear charge on the corresponding atom is increased by 1. On C-1s excitation, therefore, the residual molecular core of CO is similar to the core of the NO molecule, *i.e.* the X-ray spectrum of CO and the valence electron spectrum of NO should have similar structures [$(Z+1)$ *analogy*].

The core electrons to be excited are situated very close to the nucleus. The influence of the chemical environment on this core AO largely depends on the absolute strength and the symmetry of the field produced in the vicinity of the nucleus by the directly bonded atoms. Chemical shifts of the core orbital energy and splitting of p and d AO levels

can therefore be very satisfactorily dealt with in the electrostatic *point charge model* (cf. also[4]) and with the *ligand field theory*[12].

To estimate the transition intensities, we require the behavior only of the unoccupied MOs close to the nucleus. This can be satisfactorily described in a *one-center expansion* by one of the unoccupied AOs of the atom in question. Whereas the energies of the X-ray absorption bands can usually be adequately understood in the one-electron model, the observed intensities sometimes differ considerably from those in this model. The *electron interaction* (and also the spin-orbital coupling in the case of heavier atoms) is clearly in evidence here. In the one-center model, these effects can simply be treated as in atoms[13].

In addition to the MO and ligand field models, the *pseudopotential model*[14] in particular is very helpful for an understanding of the spatial positions and energies of the virtual MOs. According to the Pauli principle, the higher orbitals must be orthogonal to the lower, occupied MOs. This quantum-mechanical phenomenon prevents the excited electron from remaining where the molecule already has an electron. This phenomenon can be described by a potential that strongly repels the excited electron at points of particularly high electron density in the molecule. The potential is known as the occupation exclusion potential or the pseudopotential. (The repulsive effect connected with the Pauli principle, which is proportional to the square of the overlap between two occupied orbitals, has nothing to do with the electrostatic Coulomb interaction, and is generally much more significant than the latter[15].)

As was mentioned above, the main possibilities for the final state of the excited electron are a) antibonding valence MOs and b) nonbonding Rydberg MOs. The core orbitals of the atom, which form the starting levels of the one-electron excitations, are nonbonding in character. In transitions to nonbonding Rydberg MOs (class b), therefore, there is little change in the bonding, so that we expect sharp absorption lines of the 0—0 type. On excitation to antibonding valence MOs (class a), on the other hand, bonds are weakened and lengthened. The shape of the absorption bands is then strongly determined by vibrational effects (*Franck-Condon model*). The *Jahn-Teller effect* must also be taken into account in the case of highly symmetrical molecules[16].

4. Examples of the Application of X-Ray Absorption Spectroscopy

4.1. Energy Standards for ESCA Measurements

As was mentioned earlier, it is difficult to obtain accurate absolute energy values by the ESCA method. It is best to mix the gas under investigation with a reference gas whose ionization potential is accurately known. Suitable gases for this purpose are the inert gases, for which accurate X-ray absorption spectra have been recorded (*e.g.* [17, 18]).

Figure 4 shows an X-ray absorption spectrum of argon at excitation energies in the region of 250 eV[17]. The lines correspond to transitions of a $2p_{1/2}$ and of a $2p_{3/2}$ core electron to the unoccupied *n*s Rydberg AOs[19]. The energies of the

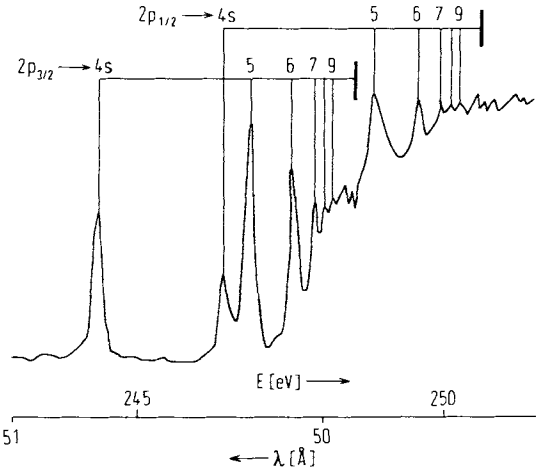


Fig. 4. Ar2p X-ray absorption spectrum [17, 19].

Rydberg orbitals can be represented very accurately by the "Rydberg formula":

$$\varepsilon_n = 13.605/(n - \delta)^2 \text{ [eV]} \quad (2)$$

where δ is an empirical constant. According to eq. (1), the measured energies ΔE_n of the absorption lines should then be given by the formula

$$\Delta E_n = BE_{2p} - \varepsilon_n \quad (2a)$$

if the two parameters δ and BE are suitable chosen. BE_{2p} is the desired ionization energy of a 2p electron, which is also known as the 2p *b*inding *e*nergy. An example is shown in Table 1.

Table 1. 2p excitations in the X-ray absorption spectrum of argon gas. ΔE_n = excitation energy.

Initial level:	$2p_{3/2}$		$2p_{1/2}$	
Final level	ΔE_n [eV]		ΔE_n [eV]	
	exp.	calc. with $\delta = 2.15$ and $BE = 248.53$ eV	exp.	calc. with $\delta = 2.15$ and $BE = 250.57$ eV
4s	244.42	244.55	246.47	246.59
5s	246.89	246.86	248.93	248.90
6s	247.61	247.61	249.65	249.65
7s	247.94	247.95	249.99	249.99
8s	248.13	248.13	250.18	250.17
9s	248.25	248.24	250.28	250.28

It is possible in this way to determine core electron binding energies (= ionization potentials) with an accuracy of about 10^{-3}—10^{-4} by extrapolation of X-ray absorption Rydberg series.

4.2. Core Electron Binding Energies of Molecules. Charge Distributions

The Rydberg spectra of molecules are more complicated than those of atoms, on account of the lower symmetry. A necessary condition for the determination of ionization potentials from X-ray spectra by extrapolation is obviously that it should be possible to assign the measured lines correctly. This presents no difficulty if a $(Z+1)$-analogous valence electron Rydberg

spectrum is known. As an example, Table 2 shows a comparison of the C1s X-ray absorption spectrum of CO[20] with the valence electron Rydberg spectrum of NO[21].

Table 2. C1s excitations of CO and optical Rydberg levels of NO.

XUV spectrum of CO [a], peak energies [eV]	Rydberg orbital	Rydberg spectrum of NO [21], energies [eV]	Energy differences
289.4_3	3s	5.48	283.9_3
289.7_4	3s*	5.77	283.9_7
290.0_5	3s**	6.06	283.9_9
290.3_1	$3p_\pi$	6.49	283.8_2
290.5_7	$3p_\sigma$, $3p_\pi^*$	6.61, 6.79	$283.8_7 \pm 0.09$
290.8_8	$3p_\sigma^*$	6.89	283.9_9
291.6_2	4s	7.55	284.0_7
291.8_8	3d, 4s*	7.78, 7.84	$284.0_5 \pm 0.03$
292.1_0	$4p_{\pi,\sigma}$, 3d*	7.97—8.07	$284.0_8 \pm 0.05$
292.3_9	$4p_{\pi,\sigma}^*$, 5s	8.26—8.33	$284.0_9 \pm 0.04$

[a] The energies were obtained from the spectrum in [20].
[b] * and ** denote respectively single and double vibrational excitation in the final state.

The Rydberg spectra in the X-ray region and in the normal UV thus correspond to within about 0.1 eV. The X-ray absorption Rydberg series assigned in this way can be extrapolated as in the case of the atoms. In this case the C1s binding energy is found to be 293.4 ± 0.2 eV. Addition of the mean energy difference from the last column in Table 2 to the valence electron ionization potential of NO gives practically the same value for the C1s ionization potential, *i.e.* 293.3 ± 0.1 eV. The N1s ionization potential of the N_2 molecule has been found in a similar manner from its X-ray spectrum, the value obtaining being 409.5 ± 0.1 eV[22].

Rydberg lines have also been resolved in the X-ray spectra of a large number of other molecules. However, no $(Z+1)$-analogous valence electron spectra are known in any of these cases. We have nevertheless been able to assign the X-ray absorption Rydberg spectra of most of the molecules (though not always with absolute certainty[23–26]) with the aid of qualitative models, which were partly supported by *ab-initio* SCF calculations[23]. Our assignments of the spectra[23, 26] differ in part from those in the original experimental work, but reassurance is provided by the fact that this has little influence on the *binding energies* obtained by extrapolation. (H_2S is an exception, see[23].)

Even if the Rydberg excitations, which are generally weak, can no longer be resolved or cannot be observed at all, it is still possible to obtain certain information about the core electron binding energies. For example, from the well-resolved S2p spectrum of SF_6, the energies of the two lowest unoccupied valence MOs are found to be -8.5 eV and -3.3 eV[26]. The S1s spectrum shows lines at 2481 eV and 2486 eV, but no Rydberg series[27]. From these data, the S1s binding energy is found to be $2489\,{}^1/_2$ eV.

The core electron binding energies derived by the author in this and similar ways from experimental spectra are shown in Table 3. Some uncertainty always exists in the last decimal place. The results are compared with reliable ESCA data. The agreement is satisfactory except in the cases of CO and GeH_4, where the differences found are 3 and 5 eV respectively, which are well outside the expected accuracy of the methods.

From the chemical shifts of the ionization potentials of atoms in various molecules, it is possible to deduce the *charges* on these atoms; this was discussed in detail by *Siegbahn* and *Nordling*[4]. A simple electrostatic model is generally sufficient. For this purpose we numbered the atoms of an $(N+1)$-atomic molecule, assigning the number 0 to the atom to be ionized. A partial charge of $+q_i$ units on the atom i at a distance R_i (in bohr) from the atom 0, according to *Coulomb*'s law, increases the ionization potentials *(IP)* of the atom 0 by $\Delta IP = e^2 \cdot q_i / R_i$. On grounds of electroneutrality, a partial charge of exactly $\sum_{i=1}^{N} q_i$ must be missing from the valence shell of the atom 0. If the interaction energy between a valence electron v of the atom 0 and the core electron c to be ionized is J_{vc} (in a.u.), therefore, the molecular ionization potential of the atom 0 has a chemical shift of

$$\Delta IP = 27.2\,\text{eV} \times \sum_{i=1}^{N} \left(\frac{1}{R_i} - J_{vc} \right) \times q_i$$

with respect to a free atom.

For example, the ionization potential (Xe $4d_{5/2}$) is 67.55 eV in free xenon but 70.4 eV in XeF_2 (see Table 3), *i.e.* $\Delta IP = 2.85$ eV. With $R_1 = R_2 = \text{Xe—F} = 3.75$ bohr, $J_{4d,5p} = 0.43$, and the assumption that the charges on the two fluorine atoms are equal, one obtains $q_1 = q_2 = -1/3$, *i.e.* the charge distribution in XeF_2 can be described by $F^{-1.3}$—$Xe^{+2.3}$—$F^{-1.3}$[46].

4.3. Properties of Radicals

4.3.1. The CF Radical

In the last section we used the valence electron spectrum of NO to obtain information about the C1s spectrum of CO, in particular with regard to the assignment of the recorded bands. Conversely, we shall now deduce information about the CF radical from the O1s spectrum of CO.

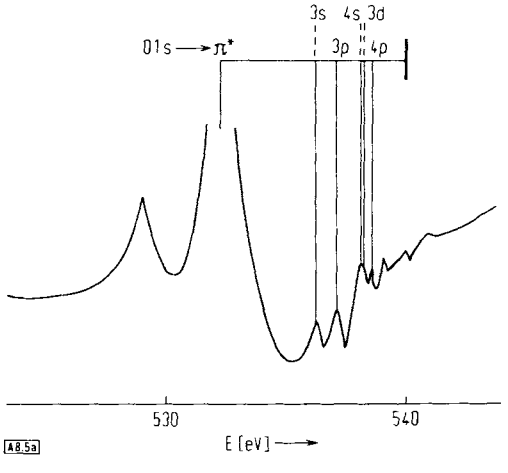


Fig. 5a. O1s X-ray absorption spectrum of CO [20].

The experimental spectrum[20] is shown in Figure 5a, with an assignment by the author[47], while Figure 5b shows a schematic potential curve diagram. The excitation of an O1s electron to Rydberg MOs or to the ionization continuum should cause practically no change in the force constant and the length of the bond. At most, *e.g.* the equilibrium distance in CO^+, as in the $(Z+1)$-analogous CF^+ (because of the

Table 3. Core electron binding energies (*IP*) of some molecules.

Atom	Core AO	Molecule	X-ray absorption spectrum	*IP* [eV]	ESCA value
B	1s	B_2H_6	[36]	197	166.5 [68]
		BCl_3	[34, 36]	199	199.8 [68]
		BF_3	[34, 36]	203½	202.8 [68]
C	1s	sp^3-HC [a]	[28]	290.6	290.3–290.8 [39, 40]
		sp^2-HC [a]	[28]	291.0	290.4–290.6 [39]
		CO [b]	[20]	293.3	296.2 [42]
N	1s	N_2	[22]	409.5	409.9 [41]
		NF_3	[35]	414	
O	1s	CO [b]	[20]	539.8	542.6 [42]
		CO_2	[28]	541½	540.8 [41] [c]
		O_2	[20]	543½	543.1, 544.2 [41]
F	1s	BF_3	[35]	695?	694.8 [68]
		SiF_4	[29]	695	
		SF_6	[43]	696	694.6 [41]
Si	1s	$SiCl_4$	[31]	1850	
	2s	SiH_4	[37]	156½	
		$SiCl_4$	[30]	160	
		SiF_4	[29]	161	
	$2p_{3\,2(1\,2)}$	SiH_4	[37]	106.8 (107.4)	107.1 [40]
		$Si(CH_3)_4$	[30]	107	105.8 [40]
		$SiCl_4$	[30]	110	110.2 [40]
		SiF_4	[29, 37]	113	111.5 [40]
P	2s	PH_3	[37]	194	
	$2p_{3\,2(1\,2)}$	PH_3	[37]	137.0 (137.9)	
S	1s	H_2S	[27]	2477½	
		SOF_2	[38]	2485	
		SF_6	[27]	2489½	
	2s	SF_6	[45]	245	244.7 [41]
	$2p_{3\,2(1\,2)}$	H_2S	[32, 37]	170.4 (171.6)	170.2 (171.5) [41]
		CS_2	[38]	171 (172)	169.8 (171.1) [41]
		SO_2	[38]	175 (176)	174.8 (176.1) [41]
		SF_6	[20]	180.6 (181.8)	180.4 (181.7) [41]
Cl	$2p_{3\,2(1\,2)}$	HCl	[37]	207.4 (209.0)	
		BCl_3	[34]	207	207.0 [68]
Ge	$3p_{3\,2(1\,2)}$	GeH_4 [b]	[37]	128½ (133½)	123.7 [40]
Te	$4d_{5\,2(3\,2)}$	Te_2	[33]	48 (49½)	
I	$4d_{5\,2(3\,2)}$	I_2	[24]	57.2 (58.9)	
Xe	$4p_{3\,2}$	XeF_2	[25]	148.4	
		XeF_4	[25]	151.0	
	$4d_{5\,2(3\,2)}$	XeF_2	[25]	70.4 (72.4)	70.5 (72.5) [46]
		XeF_4	[25]	72.9 (74.8)	73.0 (75.0) [46]

[a] HC = hydrocarbons.
[b] Unsatisfactory agreement between X-ray absorption value and ESCA value, possibly due to inaccurate calibration of the XUV spectrometer.
[c] The more recent ESCA value of *Johansson* [69] of 541.3 eV agrees considerably better with our value.

higher effective nuclear charge of O^+ or F in relation to the O atom), might be a few percent smaller than in CO. The first line[47] in the CO spectrum corresponds to the transition of the O1s electron to the lowest unoccupied MO of the antibonding π^* type. The correspondingly excited CO molecule will therefore have a slightly greater equilibrium internuclear distance and a smaller force constant, as also will the CF molecule in its ground state. The maximum approximately corresponds to the vertical transition (see Fig. 5b), which according to the Franck-Condon model, is displaced by $\varepsilon \approx \Delta^2/5.8h\nu$ toward higher energies in relation to the 0—0 transition (Δ = half-width of the absorption coefficient $\mu(E)$; $h\nu$ = vibrational quantum). Finally, it must also be taken into account that the $^2\Pi$ ground state of the CF molecule corresponds in its energy to the mean of the $^1\Pi$ and $^3\Pi$ states of the (O1s→π^*)-excited CO molecule, and is therefore lower than the observed $^1\Pi$ state of CO by the value of the exchange integral K_{O1s,π^*}. One thus obtains the following information about the CF radical:

1. The ionization potential is 9 eV. This confirms the values given by *Carroll*[48] (8.9 eV) and *Berkowitz*[49] and *Wahl*[51a] (9.2 eV), while the higher values in the range from 9.6 to 13.8 eV found by other authors[50] may be rejected.

2. An equilibrium distance of 1.3 Å and a first excitation energy to the lowest Rydberg state (3s) of 5⅓ eV are in agreement with spectroscopic measurements[48, 51] and theoretical calculations[51a].

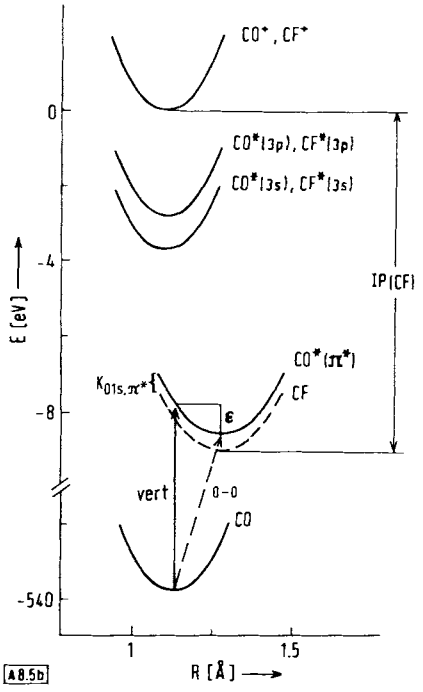


Fig. 5 b. Potential curve diagram (schematic) of CO (on core electron excitation) and CF (on valence electron excitation).

3. Higher Rydberg excitations are predicted at 6.2 eV (3p), 7.2 eV (4s), 7.4 eV (3d), 7.7 eV (4p), *etc.* Recently, *Matthews*[70] measured a band system of CF at 6.4 eV which indeed belongs to the $3p\pi\,^2\Pi$ Rydberg state.

4.3.2. The OF Radical

It should be possible to obtain information about the little-known OF radial from the O1s spectrum of O_2. The spectrum of oxygen is theoretically particularly interesting, since this is the first and so far the only case (with the exception of the homologous Te_2[33]) in which the electron interaction not only influences the intensities of the lines but also has a considerable effect on their positions, so that the spectrum can no longer be interpreted in the one-electron model.

The excited O1s electron has the half-occupied π_g MO and the strongly antibonding σ_u^* MO available in the valence shell of the O_2 molecule. The $(O1s \rightarrow \pi_g)$ excitation leads to the electronic configuration $(1s^1 \ldots \pi_g^3)$, to which the four $^{1,3}\Pi_{g,u}$ molecular states belong; of these however, on the basis of the selection rules, only the $^3\Pi_u$ state is optically attainable from the $^3\Sigma_g^-$ ground state of O_2. Of the 16 states belonging to the configuration $(1s^1 \ldots \pi_g^2 \sigma_u^*)$, only the two $^3\Sigma_u^-$ states, which differ in the coupling of the four electron spins, can be reached. If two-electron excitations did not play any part, the three transitions mentioned would be the only non-Rydberg excitations that should appear in the X-ray absorption spectrum of O_2. In addition to the measured energies, Table 4 shows the corresponding assignment of the lines, which is in agreement with the energies and intensities of the X-ray spectrum[26] and with the ionization potentials from ESCA measurements (see Table 3).

On the basis of these data, a potential curve diagram of O_2 was drawn in Figure 6, and potential curves of OF were then plotted in the diagram. From the figure we obtain an adiabatic ionization potential of 12 eV and a vertical ionization potential of $12^1/_2$ eV. *Wahl et al.*[52] have carried out an *ab-initio*

Table 4. O1s spectrum of O_2.

Peak energies [eV]	Assignment
531.9	$(1s^2 \ldots \pi^2)^3\Sigma_g^- \rightarrow (1s^1 \ldots \pi^3)^3\Pi_u$
534.9	$\rightarrow (1s^1 \ldots [\pi^2\sigma^{*2}\Sigma^-])^3\Sigma_u^-$
536.6$_5$	$\rightarrow (1s^1 \ldots [\pi^2\sigma^{*2}\Sigma^-])^3\Sigma_u^-$
539.7	$\rightarrow (1s^1 \ldots \pi^2 \cdot 3s.p)$
541.9	$\rightarrow (1s^1 \ldots \pi^2 \cdot$ higher Rydberg MOs)

calculation for the CF molecule. From this calculation and the discussion of several experimental results, they propose a value

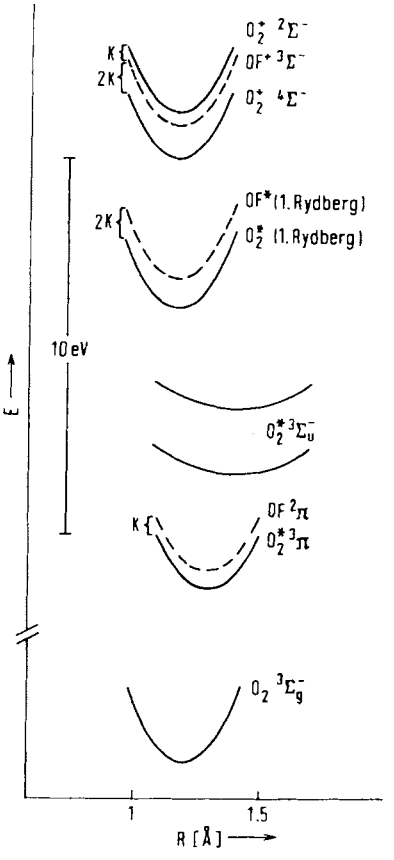


Fig. 6. Potential curve diagram (schematic) of O_2 (— · —) and OF (– – –)

of 13.1 eV for IP_{vert}. This value seems rather high, whereas the estimate of $IP_{ad} = 12.2$ eV by *Price et al.*[53] agrees well with our value. The first Rydberg excitation of CF should appear in the region of $7^2/_3$ eV.

4.3.3. The ArH Radical

Figure 7 shows the Cl 2p absorption spectrum of HCl[37] In addition to the indicated Rydberg lines, there is a very broad band at 200—204 eV, which is due to the transition to the antibonding σ^* MO[23]. If the corresponding potential curve is given by $V(R)$, the absorption coefficient μ can be represented parametrically in the semiclassical Franck-Condon model as a function of the excitation energy E by

$$\mu = \frac{\text{const} \times E}{\exp\left(M\left(\frac{\omega}{\hbar}\right)(R-R_0)^2\right)E'(R)}$$

$$E = V(R) - 0.5\,M\,\omega^2(R-R_0)^2$$

where M, ω, and R_0 are the reduced mass, the vibration frequency, and the equilibrium distance of HCl, and E' is the derivative dE/dR. $V(R)$ can be determined by fitting of μ to the experimental curve.

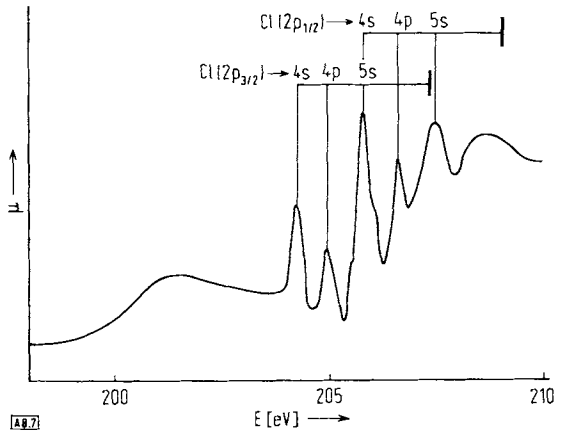


Fig. 7. Cl2p X-ray absorption spectrum of HCl [23, 37].

The result is shown in Figure 8. The $(Z+1)$-analog of this repulsive state is ArH in the ground state, whose potential curve is of interest for the interpretation of molecular collision

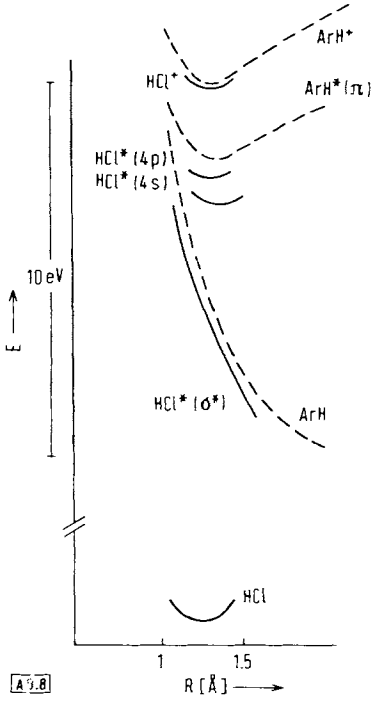


Fig. 8. Energies of HCl on $Cl2p_{3/2}$ excitation from X-ray absorption spectroscopic data (———) and potential curves of ArH obtained by *ab-initio* calculation of *Vasudevan* [23a] (– – – – –).

experiments with H and H_2 in excited states. For comparison, Figure 8 shows several potential curves found by *Vasudevan*[23a] for the ArH system by quantum-chemical *ab-initio* calculations.

4.3.4. The NH_4 and PH_4 Radicals

As a final example we shall discuss the neutral radicals of the onium ions. In contrast with the ions, practically nothing is known about the radicals. For example, it has not yet been possible even to show conclusively that H_3O and NH_4 can exist[54]; PH_4 was recently identified for the first time, though not as the free molecule, but trapped in a krypton matrix[55].

By X-ray absorption spectroscopy on the stable molecules CH_4, SiH_4, NH_3, and PH_3, it is now possible to obtain some information about the $(Z+1)$-analogous radicals NH_4, PH_4, OH_3, and SH_3[23]. According to this, the species mentioned should be thermodynamically unstable by about 1/2 eV toward the removal of H, while ClH_2 is much more unstable.

The fact that PH_4 has nevertheless been detected could be due to an activation barrier of several kcal/mol for the decomposition, as was predicted theoretically for H_3O[65]. According to the X-ray absorption spectrum of SiH_4, the metastable PH_4 with an internuclear distance of ≈ 1.7 Å and an ionization potential of just 5 eV would be expected to give a long-wave electronic absorption band in the IR at 1—1.5 μm and further bands of the Rydberg type in the violet with $\lambda < 450$ nm, which could be used for the further identification of PH_4.

According to earlier X-ray absorption measurements by *Chun*[28] on CH_4, one would have expected a considerable stability (≈ 1 eV) and an ionization potential of about $5\,^1/_2$—6 eV for NH_4, which would also correspond to the view of *Melton* and *Joy*[66]. However, a later measurement by *Chun*[56] on CH_4, which has been confirmed in the meantime by theoretical calculations[67], gives values of almost 2 eV less; NH_4 is thus thermodynamically (*i.e.* not necessarily kinetically) unstable, and the adiabatic ionization potential is approximately 4 eV. This agrees with calculations by *Bishop* for NH_4[54].

4.4. Electronic and Geometric Structure of Molecules

4.4.1. Xenon Hexafluoride

The XeF_6 molecule is an interesting test case for models for the prediction of molecular geometries. As an approximation, XeF_6 can be described by the ionic structure $Xe^{6+}F_6^-$. According to the LCAO-MO model, the two lone valence electrons remaining on the central atom are then in the totally symmetrical configuration $(5s)^2(5p)^0$, and an octahedral O_h geometry is expected for XeF_6 (see Fig. 9a). The electron

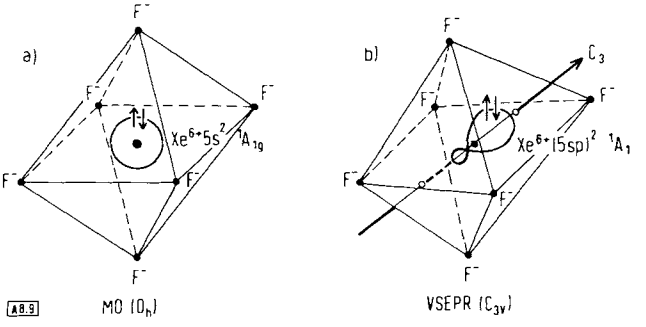


Fig. 9. Geometry and electronic structure of XeF_6. a) according to the MO model and b) according to the electron pair repulsion (VSEPR) model.

pair repulsion model[15b], on the other hand, predicts a very highly distorted geometry, in which the lone pair of electrons would be described by a doubly occupied sp hybrid orbital $(5sp^n)^2$ (see Fig. 9b).

Extensive structural investigations have been carried out on gaseous XeF_6 by electron diffraction[57]. The experimental results are not easy to interpret, but the mean symmetry of XeF_6 certainly cannot be O_h. The two most probable interpretations are as follows:

a) In principle, the electronic configuration is of the type shown in Figure 9a. However, because of the interaction with a configuration of the type shown in Figure 9b with a considerably higher energy, the asymmetric vibration modes of the XeF_6 octahedron are extremely soft, anharmonic, and coupled with one another, with the result that the molecule vibrates around the O_h symmetry, but spends by far the greater part of its time in asymmetrically distorted geometries.

b) The lowest electronically excited state of an Xe^{6+} ion is a $(5s)^1(5p)^1$ triplet. According to the three mutually perpendicular p orbitals, which are equivalent in the O_h symmetry, this state is geometrically triply degenerate. This degeneracy is lost by splitting on distortion of the octahedral geometry, and a splitting term becomes energetically more favorable (Jahn-Teller effect). It might now be possible[58] that this electronic triplet state with highly distorted geometry is situated only about 1 kcal/mol above the octahedral $5s^2$ singlet state (see Fig. 10), so that a thermodynamic equilibrium between two electronic-geometric isomers results.

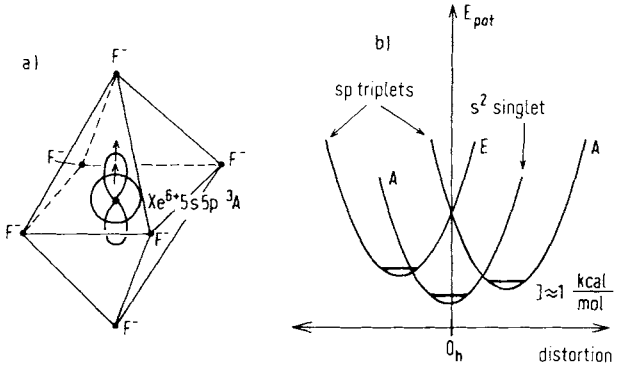


Fig. 10. a) Geometry of XeF_6 in the lowest triplet state; b) schematic potential curve diagram of XeF_6 (after *Goodman et al.*[58]).

Whereas certain hysteresis phenomena in the UV and Raman spectra[58] support possibility b, all the other experimental results (measurement of electric and magnetic moment[59]; IR, Raman, and UV spectra[58]) are compatible with both interpretations[26].

According to interpretation a (see Fig. 9a), the 5s shell is doubly occupied, whereas according to interpretation b (see Fig. 10a) the 5s shell has a vacancy in the thermally populated 5s5p state. Consequently an electronic transition $4p \rightarrow 5s$ should be found in the X-ray spectrum only in case b. Other excitations of a Xe4p electron are fundamentally ruled out; transition to the 5p-AO is forbidden by the spectroscopic selection rules, and transitions to the higher orbitals of the Rydberg type such as 3d, 6s, *etc.* are extremely weak according to the pseudopotential model[44]. To decide between cases a and b, we investigated the X-ray absorption of XeF_6 in the 150 eV region[60], but were unable to find any Xe4p excitation. In our opinion, therefore, it is more likely that XeF_6 is present in the gas phase as a single species with O_h symmetry corresponding to the simple MO model, and undergoes extremely large deformation vibrations toward the geometry predicted by the VSEPR model, rather than that an isomer mixture is present.

4.4.2. Ligand Field Splitting of Core Orbitals

If transition metal atoms are incorporated into molecules, especially complex molecules, the fivefold degeneracy of the d orbitals is eliminated by the ligand field splitting. The same effect should also occur in principle for the d core orbitals of heavy atoms, though it may be expected to be much less than in the case of d valence AOs, since the latter naturally interact much more strongly with the ligands. Whereas the resolving power of the ESCA method has not so far been sufficient for detection of the effect, it was recently detected for the first time by X-ray absorption spectroscopy on the xenon fluorides[25]. Figure 11a shows part of the X-ray absorption spectrum of XeF_2, and Figure 11b shows the one-electron level diagram derived from the spectrum. The measured split-

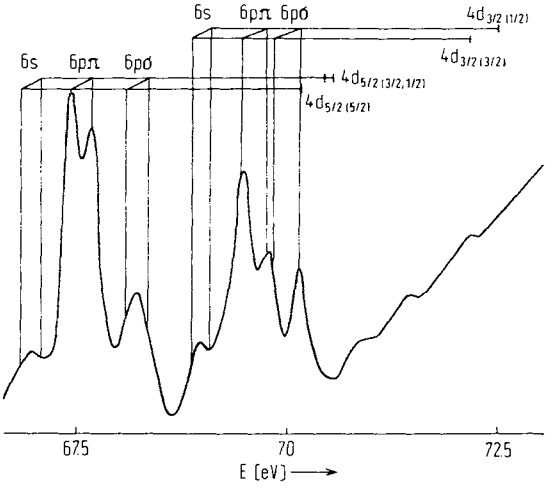


Fig. 11a. Xe4d Rydberg spectrum of XeF_2 [25].

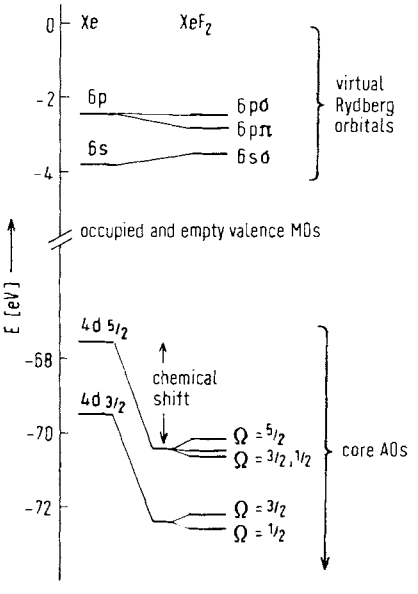


Fig. 11b. One-electron levels of xenon and XeF_2.

tings of 0.24 and 0.35 eV for the two $Xe4d_{5/2}$ and $Xe4d_{3/2}$ levels can be reproduced very satisfactorily in an electrostatic ligand field model using the charge distribution $Xe^{2/3}(F^{1/3-})_2$ as derived in Section 4.2 from the mean chemical shift of the levels. The reason why the electrostatic model is found to be quantitatively much better here than for the transition metal complexes is that overlap and delocalization effects are of practically no importance for core orbitals.

4.4.3. Structure of Virtual Orbitals

From the transitions of a core electron to the ionization continuum that can be recorded by ESCA, primary information is obtainable only for the core orbitals. On the other hand, information can be obtained about the unoccupied orbitals in the ground state, too, from the transitions of the type "core AO → virtual MO" that give rise to the X-ray absorption spectrum. The unoccupied orbitals in the ground state are not only important for excited molecular states, but also allow deductions about the occupied valence MOs and play a part in kinetic transition states.

The occupied and unoccupied MOs of the valence shell are complementary to one another. These ideas were used in Section 4.4.1 to deduce the electronic structure of the ground state of the XeF_6 molecule from its X-ray absorption spectrum. *Sadowski*[61] used a similar principle to determine the polarity of the σ bond in HCl from the X-ray absorption spectrum. The AO mixing coefficients of the MOs were obtained in this case from measured *absorption intensities*. The "experimental" result for the bonding MO was (0.5 H1s + 0.7 Cl3p), which is in satisfactory agreement with the theoretically calculated MO

The antibonding force of a virtual MO can be calculated from the recorded *band shape*. An example of this was given in Section 4.3.3 in the discussion of HCl and ArH, where we were able to deduce a dissociative potential curve from an extremely broad and asymmetric absorption band. The narrower (order of magnitude 1 eV) and nearly symmetrical bands, on the other hand, indicate that the core electron promoted to an unoccupied valence MO causes only a lengthening and weakening of the bond, as in the case of the O1s spectrum of CO discussed above or the xenon fluorides discussed in detail by *Schwarz*[25].

An interesting type of virtual orbital has been discovered in compounds in which a central atom is surrounded by several strongly electronegative ligands in a cage-like manner. The prototype of such molecules is SF_6, whose S2p spectrum is shown in Figure 12. Unusual features of this spectrum are: 1. the extremely low intensity of the Rydberg series and 2. the occurrence of fairly broad and very intense absorption bands above the ionization thresholds. Because of the high electron density in the environment of the fluorine atoms, a repulsive potential acts here on an additional electron, both because of the electrostatic Coulomb repulsion and because of the Pauli principle (pseudopotential effect)[62, 44]. Thus the six F^- ligands form a potential wall around the sulfur atom, as shown schematically in Figure 13. The low intensity of the Rydberg transitions is explained by the fact that the excited core electron of the sulfur must first tunnel through this potential wall in order to reach an outer orbital. In particular, the electron can be excited to states that correspond in their energy to a free, ionized electron, but it initially remains trapped in the interior of the molecule by the potential cage until it tunnels to freedom after a mean lifetime τ. These excitations are actually transitions to "inner" molecular orbitals, as is shown by the fact that the corresponding lines are also observed unchanged in the X-ray spectrum of solid SF_6[64], whereas experience shows that this is not so in the case of transitions to "outer" Rydberg orbitals.

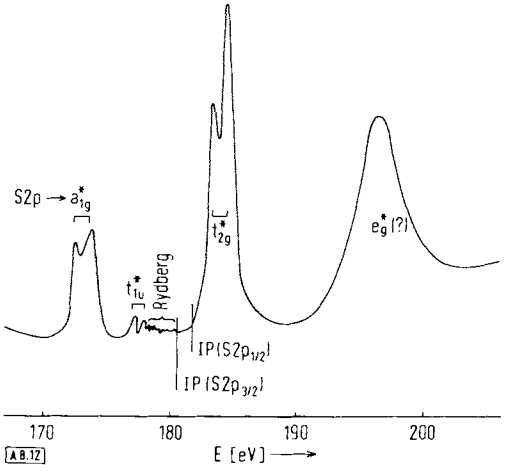


Fig. 12. S2p absorption spectrum of SF_6 [20, 45].

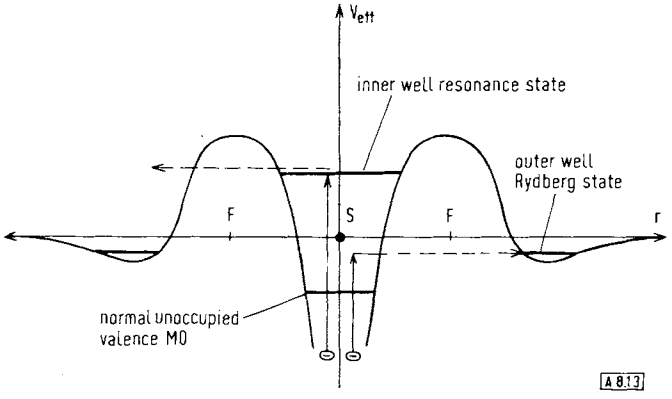


Fig. 13. Effective molecular potential in SF_6 (schematic).

The half-width of the two bands denoted by t_{2g}^* and e_g^* is not due only to the Franck-Condon broadening, but also results from the natural line width ΔE_{nat} caused by the very short lifetime τ of these resonance states in accordance with the formula

$$\Delta E_{nat} \times \tau \approx \hbar$$

A line width of 1 eV corresponds to a mean lifetime of only about 10^{-15} s, whereas the period of molecular vibrations is in the region of 10^{-13} to 10^{-14} s. The existence of the potential cage also leads to the capture of free electrons with low energies by SF_6. In fact, SF_6 has an extremely high electron capture cross section[63], which is also utilized in technical applications.

4.5. Spin-Orbit Coupling Effects

We would like to end our survey of the use of X-ray absorption spectroscopy with a brief word about spin-orbit coupling. Though *spin-orbit splitting of core orbitals* is of interest, knowledge about this splitting is rather scarce at present. Table

5 shows the spin-orbit splittings derived from the X-ray absorption spectra of the molecules mentioned in Table 3.

Table 5. Spin-orbit splitting of core orbitals of bound atoms.

Atom	AO	ΔE [eV]
Si	2p	0.6_2
P	2p	0.9_0
S	2p	1.1_5
Cl	2p	1.6_0
Ge	2p	31.4
	3p	≈ 5
Te	4d	1.48
I	4d	1.68
Xe	4d	1.93

In the case of the 4d orbital of xenon, an accurate X-ray absorption spectroscopic results exists for elementary xenon[18]: 1.97 eV. Though the Xe4d AO is a relatively high core orbital and is already appreciably influenced by the strongly polar bonds in the xenon fluorides (cf. the ligand field splittings indicated in Section 4.4.2), the difference in spin-orbital splitting between free and bound xenon is practically no greater than the experimental uncertainty of a few 10^{-2} eV. The 2% lower value for the molecules at most indicates a very slight delocalization of the Xe4d AOs in the molecule. In any case, it may be assumed in general that spin-orbit splitting of atomic core orbitals is independent of the chemical environment, and this is why the molecule in question has not been indicated in Table 5.

Spin-orbit couplings in the valence orbitals of molecules are naturally much smaller, and they are therefore often disregarded. For example, there have so far been no *ab-initio* calculations for molecules with heavy atoms in which the spin-orbit coupling was explicitly taken into account. The significance of spin-orbit coupling to important chemical problems such as stability, reactivity, and polarity of bonds is not very clear. In this connection, growing interest is being shown in the measurement of the spin-orbit splitting of unoccupied valence MOs. An effect of this type has so far been detected by X-ray absorption spectroscopy only for XeF_4[25] and XeF_6[60]; according to this work, the doubly and triply degenerate unoccupied valence orbital of the e_u or t_{2u} type has a spin-orbital splitting of 0.8 to 0.9 eV, respectively.

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[1] *J. Bergengren*, Z. Phys. *3*, 247 (1920); *A. E. Lindh*, *ibid.* *6*, 303 (1921).

[2] *R. H. Messner*, Z. Phys. *85*, 727 (1933); *T. Magnusson*, Nova Acta Regiae Soc. Sci. Upsal. *11*, No. 3 (1939).

[3] Examples: *K. Böke*, Z. Phys. Chem. NF *10*, 45, 59 (1957); *11*, 326 (1957); *E. Kauer*, *ibid.* *6*, 105 (1956); *E. O. Fischer*, *G. Joos*, and *E. Vogy*, *ibid.* *18*, 80 (1958); *G. Joos* and *K. H. Peter*, *ibid.* *18*, 74 (1958); *A. Schneider*, *ibid.* *31*, 249 (1962); *G. Fieldler*, *ibid.* *37*, 79 (1963).

[4] *K. Siegbahn et al.*, Nova Acta Regiae Soc. Sci. Upsal. *20*, 2 (1967) "ESCA volume"; *C. Nordling*, Angew. Chem. *84*, 143 (1972); Angew. Chem. internat. Edit. *11*, 83 (1972).

[5] *S. Flügge*: Handbuch der Physik. Vol. 30. Springer, Berlin 1957.

[6] *J. A. R. Samson*: Techniques of Vacuum Ultraviolet Spectroscopy. Wiley, New York 1967.

[7] *T. J. Peterson* and *D. H. Tomboulian*, Phys. Rev. *125*, 235 (1962).

[8] *A. P. Lukirski*, Izv. Akad. Nauk SSSR, Ser. Fiz. *25*, 913 (1961); *A. P. Lukirski* and *V. A. Fomitschew*, Opt. Spektrosk. *19*, 800 (1965).

[9] *R. P. Godwin*, Springer Tracts Mod. Phys. *51*, 1 (1969); *W. Hayes*: Contemp. Phys. *13*, 441 (1972); *K. Codling*, Rep. Progr. Phys. *36*, 541 (1973).

[10] *D. H. Tamboulian* and *P. L. Hartmann*, Phys. Rev. *102*, 1423 (1965); *D. H. Tomboulian* and *E. D. Bedo*, J. Appl. Phys. *29*, 804 (1958); *K. Codling* and *R. P. Madden*, *ibid.* *36*, 380 (1964); *R. Haensel* and *C. Kunz*, Z. Angew. Phys. *23*, 276 (1967); *C. Kunz*, *R. Haensel*, and *B. Sonntag*, J. Opt. Soc. Amer. *58*, 1415 (1968); *C. Gähwiller*, *F. C. Brown*, and *H. Fujita*, Rev. Sci. Instrum. *41*, 1275 (1970).

[11] *G. V. Marr* and *I. H. Munro*: Proceedings of the International Symposium for Synchrotron Radiation Users, Daresbury Nuclear Physics Laboratory 1973.

[12] *H. L. Schäfer* and *G. Gliemann*, Einführung in die Ligandenfeldtheorie. Akademische Verlagsgesellschaft, Frankfurt 1967; *J. S. Griffith*: The Theory of Transition-Metal Ions. Cambridge University Press, London 1961.

[13] *E. U. Condon* and *G. H. Shortley*: The Theory of Atomic Spectra. Cambridge University Press, London 1935; *J. C. Slater*: Quantum Theory of Atomic Structure. McGraw-Hill, New York 1960.

[14] *W. H. E. Schwarz*, Theor. Chim. Acta *11*, 307 (1968); *J. D. Weeks*, *A. U. Hazi*, and *S. A. Rice*, Advan. Phys. Chem. *16*, 283 (1969).

[15] a) *C. G. Jorgensen*: Modern Aspects of Ligand Field Theory, North Holland, Amsterdam 1971; b) *R. J. Gillespie*: Angew. Chem. *70*, 885 (1967); Angew. Chem. internat. Edit. *6*, 819 (1967).

[16] *G. Herzberg*: Molecular Spectra and Molecular Structure. Vol. I, II. Van Nostrand, Princeton 1950, 1956.

[17] *M. Nakamura et al.*, Phys. Rev. Lett. *21*, 1303 (1968).

[18] *K. Codling* and *R. P. Madden*, Phys. Rev. Lett. *12*, 106 (1964); Appl. Opt. *4*, 1431 (1965); *W. S. Watson* and *F. J. Morgan*, Proc. Phys. Soc. London (At. Mol. Phys.) *2*, 277 (1969).

[19] In argon the *ns*-Rydberg levels are accidently almost identical with the $(n-2)$d levels (for $n \geq 5$), so that the respective peaks, strictly speaking, correspond to two transitions each: $2p \rightarrow ns$ and $2p \rightarrow (n-2)d$.

[20] *M. Nakamura et al.*, 3rd Int. Conf. VUV Rad. Phys., page 1 p A1. Tokio 1971.

[21] *G. Herzog*, *A. Lagerqvist*, and *E. Miescher*, Can. J. Phys. *34*, 622 (1956); *R. F. Barrow* and *E. Miescher*, Proc. Phys. Soc. London *A 70*, 219 (1957); *K. Dressler* and *E. Miescher*, Astrophys. J. *141*, 1266 (1965).

[22] *M. Nakamura et al.*, Phys. Rev. *178*, 80 (1969).

[23] *W. H. E. Schwarz*, to be published.

[23a] *K. Vasudevan*, personal communication.

[24] *F. J. Comes*, *U. Nielsen*, and *W. H. E. Schwarz*, J. Chem. Phys. *58*, 2230 (1973).

[25] *F. J. Comes*, *R. Haensel*, *U. Nielsen*, and *W. H. E. Schwarz*, J. Chem. Phys. *58*, 516 (1973).

[26] *W. H. E. Schwarz*, unpublished results.

[27] *R. E. LaVilla* and *R. D. Deslattes*, J. Chem. Phys. *44*, 4399 (1966).

[28] *H. Hartmann* and *H. U. Chun*, Theor. Chim. Acta *2*, 1 (1964); *H. U. Chun*, *T. K. Ha*, and *R. Mann*, Z. Phys. Chem. N. F. *47*, 313 (1965); *H. U. Chun* and *H. Gebelein*, Z. Naturforsch. *22a*, 1813 (1967); *H. U. Chun*, *ibid.* *23a*, 1415 (1968).

[29] *A. S. Vinogradow* and *T. M. Simkina*, Opt. Spektrosk. *31*, 542 (1971).

[30] *V. A. Fomitschev*, *T. M. Simkina*, *A. S. Vinogradov*, and *A. M. Evdokimov*, Zh. Strukt. Khim. *11*, 676 (1970); *T. M. Simkina* and *A. S. Vinogradov*, J. Physique *32*, C4-3 (1971).

[31] *D. L. Mott*, Phys. Rev. *144*, 94 (1966).

[32] *A. S. Vinogradov* and *T. M. Simkina*, Opt. Spektrosk. *31*, 685 (1971).

[33] *R. Haensel*, *K. Radler*, *B. Sonntag*, and *G. Zimmerer*, Verh. Deut. Phys. Ges. *1973*, No. 5.

[34] *V. A. Fomitschev*, Fis. Tverd. Tela *9*, 3167 (1967); *V. A. Fomitschev* and *R. L. Barinski*, Zh. Strukt. Khim. *11*, 875 (1970).

[35] *T. M. Simkina* and *A. S. Vinogradov*, Isv. Akad. Nauk SSSR *36*, 248 (1972).

[36] *W. Hayes* and *F. C. Brown*, Proc. Phys. Soc. London (At. Mol. Phys.) *4*, L85 (1971).

[37] *W. Hayes*, *F. C. Brown*, and *A. B. Kunz*: Phys. Rev. Lett. *27*, 774 (1971); *W. Hayes* and *F. C. Brown*, Phys. Rev. *A 6*, 21 (1972).

[38] *R. E. LaVilla*, unpublished (see ref. [4]).

[39] *T. D. Thomas*, J. Chem. Phys. *52*, 1773 (1970).

[40] *W. B. Perry* and *W. L. Jolly*, Chem. Phys. Lett. *17*, 611 (1972).

[41] *K. Siegbahn et al.*: ESCA Applied to Free Molecules. North Holland, Amsterdam 1969.

[42] *T. D. Thomas*, J. Chem. Phys. *53*, 1744 (1970); *R. W. Shaw* and *T. D. Thomas*, Chem. Phys. Lett. *14*, 121 (1972).

[43] *A. S. Vinogradov*, *T. M. Simkina*, and *W. A. Fomitschev*, Zh. Strukt. Khim. *12*, 899 (1971); *R. E. LaVilla*, J. Chem. Phys. *57*, 899 (1972).

[44] *J. L. Dehmer*, J. Chem. Phys. *56*, 4498 (1972).

[45] *T. M. Simkina* and *V. A. Fomitschev*: Dokl. Akad. Nauk SSSR *169*, 1304 (1966).

[46] *S. E. Karlsson*, *K. Siegbahn*, and *N. Bartlett*, personal communication.

[47] The first band at 529eV can be interpreted neither as $^1\Sigma^- \rightarrow (O1s \rightarrow 2\pi^*)^{3,1}\Pi$ nor as $^1\Sigma^- \rightarrow (O1s \rightarrow 6\sigma^*)^1\Sigma^+$ of CO according to energy and intensity considerations. It is probably an artefact of the measurement (scattered light of another order, H_2O?).

[48] *P. K. Carroll* and *T. P. Grennan*: Proc. Phys. Soc. London (At. Mol. Phys.) *3*, 865 (1970).

[49] *T. A. Walter, C. Lifshitz, W. A. Chupka*, and *J. Berkowitz*, J. Chem. Phys. *51*, 3531 (1969).

[50] *R. I. Reed* and *W. Snedden*, Trans. Faraday Soc. *54*, 301 (1968); *G. Herzberg*, unpublished results; *C. Lifshitz* and *F. A. Long*, J. Phys. Chem. 69, 373 (1965).

[51] *T. L. Porter, D. E. Mann*, and *N. Acquista*, J. Mol. Spectrosc. *16*, 228 (1965).

[51a] *P. A. G. O'Hare* and *A. C. Wahl*, J. Chem. Phys. *55*, 666 (1971); *J. A. Hall* and *W. G. Richards*, Mol. Phys. *23*, 331 (1972).

[52] *P. A. G. O'Hare* and *A. C. Wahl*, J. Chem. Phys. *53*, 2469 (1970).

[53] *W. C. Price, T. R. Passmore*, and *D. M. Roessler*, Disc. Faraday Soc. 35, 201 (1963).

[54] *D. M. Bishop*, J. Chem. Phys. *48*, 5285 (1968); *E. Mclamud, D. Getz, S. Schlick*, and *B. L. Silver*, Chem. Phys. Lett. *15*, 591 (1972).

[55] *C. A. McDowell, K. A. R. Mitchell*, and *P. Raghunathan*, J. Chem. Phys. *57*, 1699 (1972).

[56] *H. U. Chun*, Phys. Lett. *30 A*, 445 (1969).

[57] *L. S. Bartell* and *R. M. Gavin*, J. Chem. Phys. *48*, 2460, 2466 (1968).

[58] *G. L. Goodman*, J. Chem. Phys. *56*, 5038 (1972); *H. H. Claassen, G. L. Goodman*, and *H. Kim*, *ibid. 56*, 5042 (1972).

[59] *R. F. Code, W. E. Falconer, W. Klemperer*, and *I. Ozier*, J. Chem. Phys. *47*, 4955 (1967); *W. E. Falconer, A. Büchler, J. L. Stauffer*, and *W Klemperer*, *ibid. 48*, 312 (1968).

[60] *U. Nielsen, R. Haensel*, and *W. H. E. Schwarz*, J. Chem. Phys., in press.

[61] *A. P. Sadowski, L. N. Masalov, W. M. Bertenev*, and *M. M. Murachtanov*, Teor. Eksp. Khim. 6, 502 (1970).

[62] *W. I. Nefedov*, Zh. Strukt. Khim. *11*, 292 (1970).

[63] *R. N. Compton* and *R. H. Huebner*: Advan. Radiat. Chem. *2*, 281 (1970).

[64] *D. Blechschmidt, E. E. Koch, R. Haensel, U. Nielsen*, and *T. Sagawa*, Chem. Phys. Lett. *14*, 33 (1972).

[65] *R. E. Gangi* and *R. F. Bader*, Chem. Phys. Lett. *11*, 216 (1971).

[66] *C. E. Melton* and *H. W. Joy*, J. Chem. Phys. *46*, 4275 (1967); *48*, 5286 (1968).

[67] *P. S. Bagus, M. Krauss*, and *R. E. LaVilla*, Chem. Phys. Lett. *23*, 13 (1973).

[68] *D. A. Allison et al.*, J. Electr. Spectr. *1*, 269 (1972).

[69] *G. Johansson, J. Hedman, A. Berndsson, M. Klasson*, and *R. Nilsson*, J. Electr. Spectr. *2*, 295 (1973).

[70] *C. W. Matthews*, unpublished

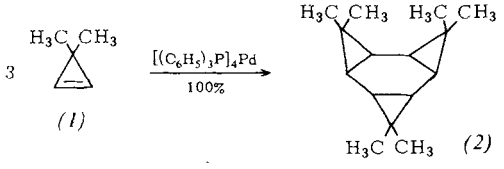
COMMUNICATIONS

Quantitative Cyclotrimerization of 3,3-Dimethylcyclopropene to "Hexamethyl-*trans*-σ-trishomobenzene"[1]

By *Paul Binger, Gerhard Schroth*, and *John McMeeking*[*]

In the course of our studies on the behavior of thermally stable unsaturated three-membered cyclic hydrocarbons in the presence of transition metal complexes[2] we have also investigated the reaction of 3,3-dimethylcyclopropene *(1)*[3] at palladium(0) catalysts. Only the cyclodimerization of 1-methylcyclopropene in the presence of palladium(II) catalysts has hitherto been described[4].

In the presence of catalytic quantities of tetrakis(triphenylphosphane)palladium(0)[5] compound *(1)* undergoes *quantitative* trimerization to crystalline hexamethyl-*trans*-σ-trishomobenzene *(2)*[1], m.p. 38 °C.



(1) *(2)*

Mass spectrometry indicates a molecular weight of 204 for *(2)*. The sharply structured IR spectrum points to a rigid carbocycle and exhibits no C=C stretching vibrations. The precise molecular structure of *(2)* follows from the ^{1}H-NMR spectrum (Fig. 1): the presence of four signals for the eighteen methyl protons in the ratio 3:6:6:3 and three signals for the six three-membered ring protons in the ratio 2:2:2 reveal a *trans* configuration (C_s symmetry). The four "*cis* protons" A,A',B,B' exhibit coupling constants of $J_{AA'} = 10.1$, $J_{AB} = 9.0$, $J_{AB'} = -0.5$, and $J_{BB'} \approx 0$ Hz (determined with the aid of the iteration program LAME; mean error 0.08 Hz). The coupling constant between the "*trans* protons" X,X' and B,B' amounts to only *ca.* 0.5 Hz owing to almost complete orthogonality; in the spectrum this coupling is recognizable only as line broadening of the two pertinent signals. The three-dimensional X-ray structure analysis[6] confirms our ^{1}H-NMR results.

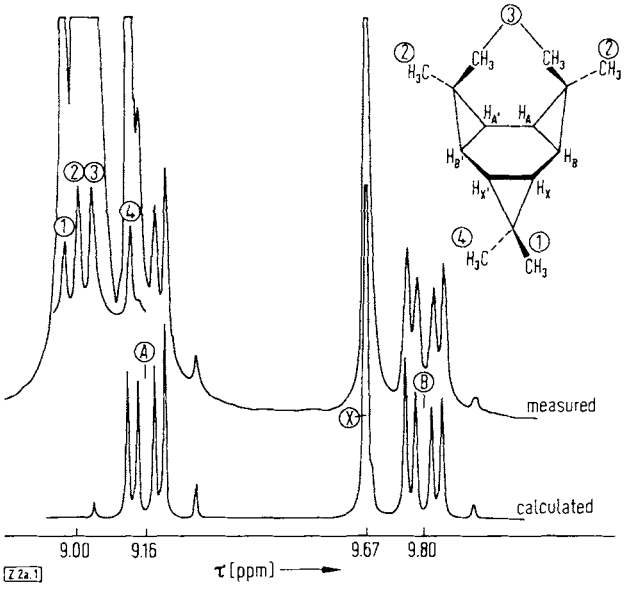


Fig. 1. ^{1}H-NMR spectrum (100 MHz; in benzene, 20 °C) of hexamethyl-*trans*-σ-trishomobenzene *(2)*.

Above *ca.* 120 °C compound *(2)* isomerizes to a homogeneous $C_{15}H_{24}$ hydrocarbon containing one C=C bond whose structure is currently under study.

To our knowledge, the cyclotrimerization of *(1)* to *(2)* is the first example of a smooth cyclohexane ring formation from an alkene and provides a new entry to "σ-trishomobenzene" derivatives[7].

In the presence of triphenylphosphane-modified nickel(0) complexes, compound *(1)* undergoes preferential dimerization

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to *trans*-3,3,6,6-tetramethyltricyclo[3.1.0.0^{2,4}]hexane; a small amount of *(2)* is also formed.

Procedure:

Compound *(1)* (8 g, 118 mmol) is added dropwise over 2 h to a stirred solution of tetrakis(triphenylphosphane)palladium(0) (0.41 g, *ca.* 0.36 mmol) in benzene (25 ml) with intermittent cooling to 40–45 °C. After stirring for another 2 h all the components that are volatile at 0.1 torr are drawn off and the residue fractionally distilled. Apart from benzene, one obtains 8 g (100%) of *(2)* (99.2% pure according to GC), b.p. 76 °C/0.5 torr, m.p. 38 °C.—The catalyst which is recovered as a brownish yellow powder is still active for further trimerizations.

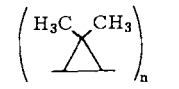
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[1] 3,3,6,6,9,9-Hexamethyl-*cis,cis,trans*-tetracyclo[6.1.0.0^{2,4}.0^{5,7}]nonane.

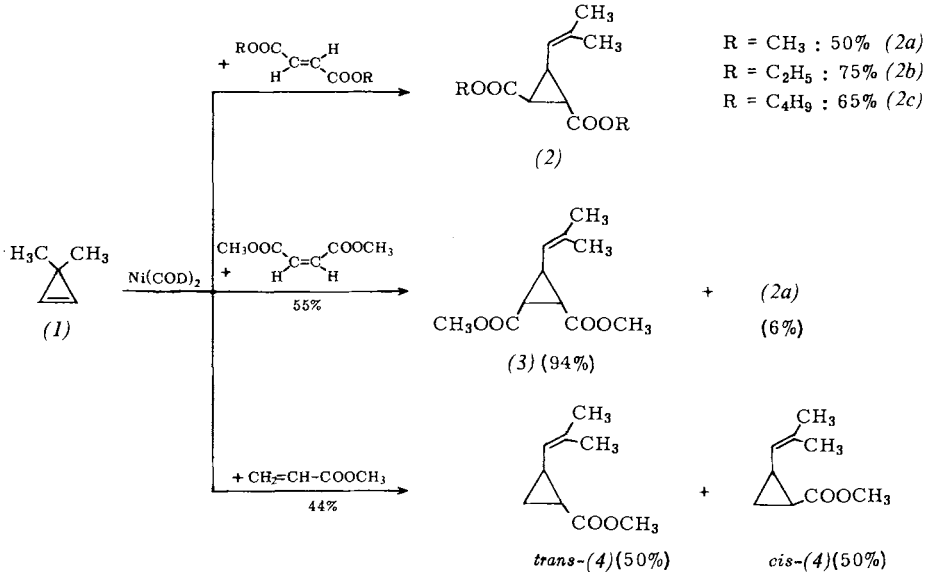
[2] *P. Binger*, Angew. Chem. *84*, 352 (1972); Angew. Chem. internat. Edit. *11*, 309 (1972); Synthesis *1973*, 427; *P. Binger* and *J. McMeeking*, Angew. Chem. *85*, 1053 (1973); *86*, 518 (1974); Angew. Chem. internat. Edit. *12*, 995 (1973); *13*, 466 (1974).

and the cyclotrimerization of *(1)* at palladium(0) complexes[4] have been reported.

We found that with nickel(0) catalyst, *e.g.* Ni(COD)$_2$[5], compound *(1)* affords benzene-soluble oligomers consisting mainly of chains of the type



(^{1}H-NMR). Triphenylphosphane-modified nickel(0) compounds preferentially convert *(1)* into a cyclodimer[4]. On the other hand, reaction of *(1)* with an excess of dialkyl fumarate in the presence of nickel(0) catalysts results in codimerization to give up to 75% yield of pure dialkyl 3-(2-methyl-1-propenyl)cyclopropane-*trans*-1,2-dicarboxylate *(2)*. In contrast, dimethyl maleate and *(1)* afford *ca.* 94% pure dimethyl *trans*-3-(2-methyl-1-propenyl)cyclopropane-*cis*-1,2-dicarboxylate *(3)* in 55% yield together with 6% of *(2a)* which is formed owing to ready C=C isomerization at nickel(0) catalysts.



[3] *P. Binger*, Synthesis *1974*, 190.

[4] *F. J. Weigert*, *R. L. Baird*, and *J. R. Shapley*, J. Amer. Chem. Soc. *92*, 6630 (1970).

[5] *E. O. Greaves*, *C. J. L. Lock*, and *P. M. Maitlis*, Can. J. Chem. *46*, 3879 (1968).

[6] *C. Krüger* and *P. J. Roberts*, Cryst. Struct. Commun., in press.

[7] Other preparations of *trans*-σ-trishomobenzene compounds are given by: *D. L. Dalrymple* and *S. P. Taylor*, J. Amer. Chem. Soc. *93*, 7098 (1971); *M. Engelhard* and *W. Lüttke*, Angew. Chem. *84*, 346 (1972); Angew. Chem. internat. Edit. *11*, 310 (1972); *H. Prinzbach* and *R. Schwesinger*, *ibid. 84*, 988 (1972) and *11*, 940 (1972), resp.

Codimerization of 3,3-Dimethylcyclopropene with Ethylenecarboxylic Esters at Nickel(0) Catalysts

By *Paul Binger* and *John McMeeking*[*]

After methylenecyclopropane[1], we have now also investigated the behavior of 3,3-dimethylcyclopropene *(1)*[2] in the presence of nickel(0) complexes. So far only the cyclodimerization of 1-methylcyclopropene at palladium(II) catalysts[3] Methyl acrylate and *(1)* react at a nickel(0) catalyst to form a *ca.* 44% yield of an equimolar mixture of methyl *cis*- and *trans*-2-(2-methyl-1-propenyl)cyclopropanecarboxylate *(4)* alongside *ca.* 10% of a 2:1 mixed trimer [exp. MW 240 (MS)] of acrylic ester and *(1)*. Higher molecular weight products are also formed.

The composition and structure of the substituted alkyl cyclopropanecarboxylates *(2)* to *(4)* were deduced from their IR, mass, and above all their ^{1}H-NMR spectra. The *cis* or *trans* orientation of the substituents in *(3)* and *(4)* followed from the position of the vinyl proton signal[6] (*e.g. trans-(4)*: $\tau = 5.40$ ppm; *cis-(4)*: $\tau = 4.92$ ppm) and from the coupling constants of the ring protons[7] (*e.g. (3)*: $J_{cis} = 8.5$ Hz; $J_{trans} = 6.2$ Hz).

The substituted cyclopropane derivatives *(2)* to *(4)* are presumably formed from *(1)* while π-bonded to nickel(0) by cleavage of the C^1—C^3 bond, possibly *via* a transient complex-bonded carbene species.

Diethyl 3-(2-methyl-1-propenyl)cyclopropane-trans-1,2-dicarboxylate (2b):

Compound *(1)* (6.4 g, 94 mmol) is added dropwise over 1.5 h to the red solution of Ni(COD)$_2$ (1.1 g, 4.2 mmol) in diethyl

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fumarate (59.8 g, 347 mmol) at room temperature. During the reaction the temperature of the mixture is kept at 35—40 °C by water cooling. After stirring for 1 h, all the components that are volatile at 115 °C/0.1 torr are distilled off to leave 2.1 g of a black viscous residue. Fractional distillation affords 42.7 g of 96% pure (GC) diethyl fumarate and 17.5 g of 93.8% pure (GC) *(2b)*, b. p. 63—65 °C/0.001 torr, which still contains diethyl fumarate (1.6%) and six other unknown compounds (4.6%).

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[1] *P. Binger*, Angew. Chem. *84*, 352 (1972); Angew. Chem. internat. Edit. *11*, 309 (1972); Synthesis *1973*, 427; *P. Binger* and *J. McMeeking*, Angew. Chem. *85*, 1053 (1973); Angew. Chem. internat. Edit. *12*, 995 (1973).

[2] *P. Binger*, Synthesis *1974*, 190.

[3] *F. J. Weigert*, *R. L. Baird*, and *J. R. Shapley*, J. Amer. Chem. Soc. *92*, 6630 (1970).

[4] *P. Binger*, *G. Schroth*, and *J. McMeeking*, Angew. Chem. *86*, 518 (1974); Angew. Chem. internat. Edit. *13*, 465 (1974).

[5] COD = 1,5-cyclooctadiene. *B. Bogdanović*, *M. Kröner*, and *G. Wilke*, Liebigs Ann. Chem. *699*, 1 (1966).

[6] *P. H. Mazzochi* and *H. J. Tamburin*, J. Org. Chem. *38*, 2221 (1973).

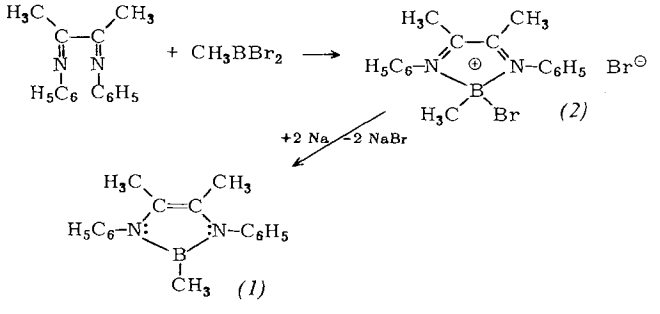
[7] *H. Günther* and *D. Wendisch*, Chem. Ber. *104*, 3914 (1971); *A. F. Bramwell*, *L. Crombie*, *P. Hemesley*, *G. Pattenden*, *M. Elliot*, and *N. F. Janes*, Tetrahedron *25*, 1727 (1969).

1,3-Diphenyl-2,4,5-trimethyl-1,3,2-diazaboroline

By *Lothar Weber* and *Günter Schmid*[*]

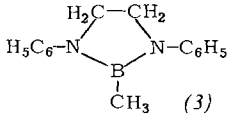
Diazaborolines are derived from pyrroles by formal isosteric replacement of a C=C by a BN group and are isoelectronic with the cyclopentadienide ion. They therefore warrant attention as potential complex ligands. The first representative of this class, 1,3-dimethyl-2-phenyldiazaboroline[1], has been described in a recent publication. We have now found a novel elegant preparation of these heterocycles in the synthesis of 1,3-diphenyl-2,4,5-trimethyl-1,3,2-diazaboroline *(1)*.

Reduction of the boronium salt *(2)* with sodium amalgam in diethyl ether affords *(1)* in about 50% yield.



(2) *(1)*

The starting material *(2)* is obtained as a reddish-brown solid, m. p. 152 °C (dec.) by reaction of *N,N'*-diphenylbiacetyldiimine with methyldibromoborane in ether. The salt is readily soluble in polar solvents; a 1.71×10^{-3} M solution in CH_3CN



(3)

displays a specific conductivity of $2.03 \times 10^{-5}\,\Omega^{-1}\,cm^{-1}$, thus indicating extensive dissociation. The structure of the cation follows from its ^1H- and ^{11}B-NMR spectra and from reduction to *(1)*.

The diazaboroline *(1)* can be isolated as a yellow liquid having the viscosity of honey, b. p. 112—115 °C/0.05 torr. It is soluble in all inert organic solvents and exhibits a pronounced tendency to crystallize; however, complete crystallization has hitherto not been observed. Cryoscopic molecular-weight determination gives a value of 244 (calc. 262.11). Compound *(1)* is extremely sensitive to air (decomposition with dark coloration).

The ^1H-NMR spectrum (C_6D_6, TMS internal standard) contains three sharp signals in the intensity ratio 3:6:10 at −0.57 (B—CH_3), −1.92 (C—CH_3), and −7.20 ppm (C_6H_5). The chemical shift ^{11}B amounts to −28.0 ppm (relative to BF_3 etherate). Comparison of this value with that of the "nonaromatic" compound *(3)*[2], *i.e.* −33.4 ppm, indicates a significantly stronger shielding of the boron atom in the ring system *(1)*.

Boronium salt (2):

CH_3BBr_2 (1.95 g, 10.0 mmol) is dissolved with cooling in anhydrous ether (100 ml) and added dropwise to vigorously stirred ether (500 ml) simultaneously with a solution of biacetyldianil (2.48 g, 10.0 mmol) in ether (100 ml). The sparingly soluble reddish brown product is filtered off, washed with ether, and dried *in vacuo*: 4.13 g of *(2)* (93.3%).

1,3-Diphenyl-2,4,5-trimethyl-1,3,2-diazaboroline (1):

Sodium amalgam (180 g, 1%) is added to a suspension of *(2)* (9.49 g, 22.5 mmol) in ether (150 ml). After stirring for 24 h at room temperature the orange-yellow solution is separated from mercury and NaBr and the ether stripped off *in vacuo*. Distillation of the oily residue at 112—115 °C/0.05 torr yields 3.03 g of *(1)* (51.3%).

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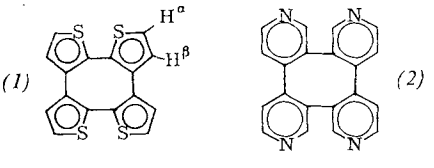
[1] *J. S. Merriam* and *K. Niedenzu*, J. Organometal. Chem. *51*, C 1 (1973).

[2] Colorless crystals, m. p. 97—98 °C, prepared from *N,N'*-diphenylethylenediamine and methyldibromoborane according to *K. Niedenzu* and *C. D. Miller*, Fortschr. Chem. Forsch. *15*, 191 (1970).

Preparation and Properties of Cycloocta[1,2-*b*:4,3-*b'*:5,6-*b''*:8,7-*b'''*]tetrathiophene[1][**]

By *Bernd Greving*, *Annegret Woltermann*, and *Thomas Kauffmann*[*]

Formal linkage of arenes[2] to macrocycles yields cyclopolyarenes. It can hardly be doubted that the heterocyclic representatives of this class will include members exhibiting pronounced nucleophilic or electrophilic activity[3] if the cyclic systems are composed exclusively of nuclei of one category, as in the cyclotetraarenes *(1)* and *(2)*[4]. Wherever this does not apply, a certain degree of compensation of the nucleophilic and electrophilic properties typical of the individual nuclei may be expected[5,6].



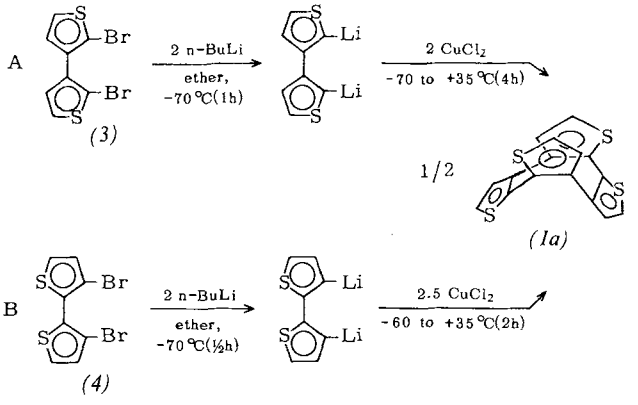
(1) *(2)*

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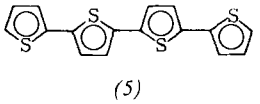
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In order to cast some light upon the situation we have synthesized the colorless cyclotetraarene *(1)* [m.p. 254 °C (from chloroform/ether 2:1)] as shown from the dibromides *(3)*[7] (route A) and *(4)*[8] (route B)[9]. The compound *(1)*, which is obtained in 25 and 18% yield, respectively, is shown to be nonplanar by molecular models; instead it has the spatial structure *(1a)*.

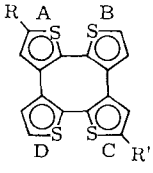


(3) *(1a)* *(4)*

According to the ^{1}H-NMR spectrum [($CDCl_3$, TMS, 100 MHz), 2 doublets at $\delta = 6.93$ (H^β) and 7.34 (H^α) (1:1); $J_{\alpha,\beta} = 5.2$ Hz] the nuclei of *(1)* are typical π-electron excess nuclei (thiophene: $\delta = 7.00$ to 7.40). They undergo mutual electronic interaction, for in the UV spectrum (10^{-4} M chloroform solution) the absorption maximum exhibits a bathochromic shift in comparison with thiophene [*(1)*: $\lambda_{max} = 278$ nm ($\varepsilon = 18000$); thiophene: $\lambda_{max} = 239$ nm ($\varepsilon = 5600$)]. Since the absorption maximum lies between that of 2,2'-bithienyl [$\lambda_{max} = 297$ nm ($\varepsilon = 12300$)] and that of 3,3'-bithienyl [$\lambda_{max} = 263$ ($\varepsilon = 19000$)], it may be assumed that the mesomerism is essentially limited to two neighboring nuclei. As in the case of the two bithienyls, the spectrum of *(1)* contains an additional strong band at 242 nm ($\varepsilon = 11000$) indicating a separate electronic transition in the individual thiophene nuclei.



(5)



(6), R = Li, R' = H
(7), R = 4-Pyrimidinyl, R' = H
(8), R = R' = 4-Pyrimidinyl

While hydrogen-lithium exchange has not yet been accomplished in open-chain tetraarene *(5)*[10], compound *(1)* could be smoothly lithiated. The reaction with 1 mol of butyllithium in THF at 0 °C (1/2 h) proceeded almost quantitatively. The monolithium compound *(6)* is probably the major product since subsequent reaction with 1.2 mol of pyrimidine (3 h at 0 °C and then 1 h at 65 °C) and oxidation of the hydrolyzed reaction products with $KMnO_4$ in acetone at 20 °C (part of the product *(7)* can already be detected prior to oxidation) afforded, apart from unchanged *(1)* (52%), the yellow monopyrimidinyl derivative *(7)* [m.p. 245—247 °C (from ethanol/chloroform 1:1); yield 79% based on reacted *(1)*] as the main product, as well as a likewise crystalline dipyrimidinyl derivative [m.p. 205—207 °C (from ethanol); yield 9% based on reacted *(1)*]. It has yet to be decided whether the second substituent in the dipyrimidinyl derivative is bonded to nucleus C as shown in *(8)* or whether it is located in the α position of nucleus B or D. The exceptionally small amounts obtained in the case of two further yellow substances (presumably also dipyrimidinyl derivatives) have so far obstructed their preparation in a pure state.

In the lithium compound *(6)*, in its pyrimidine adduct, and in *(7)*, one of the four thiophene nuclei is modified electronically by the substituent. Since dipyrimidinyl derivatives are apparently formed in much smaller quantities than the monopyrimidinyl derivative, this modification seems to be transmitted electronically to the remaining three thiophene nuclei thus preventing the second substitution.

Apart from the reservation made above for the dipyrimidinyl derivative, the structures of the new compounds are established by their spectra (MS, ^{1}H-NMR, UV) and elemental analysis.

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[1] Protophanes and Polyarenes, Part 16.—Part 15: *Th. Kauffmann* and *H.-H. Kniese*, Tetrahedron Lett. *1973*, 4043.

[2] In this communication the term "arene" refers to monocyclic aromatic hydrocarbons and corresponding heterocycles.

[3] The expressions nucleophilic and electrophilic refer here to the predominating behavior taken over the known reactions.

[4] In the cyclic systems formally composed of 2p/2π electron systems [5], the stability and tendency to undergo regeneration (after addition of reagents) strongly depend upon the number of groups used in their construction (Hückel rule). As examples of such groups we may cite —O—, —S—, —N<, >C=C<, >C=N—. In contrast, the properties of cyclopolyarenes should hardly be influenced by the number of units since the units themselves have aromatic character, and, as found for polyphenylenes [cf. *H. A. Staab* and *F. Binnig*, Chem. Ber. *100*, 293 (1967)] will no doubt generally retain it on linkage.

[5] *Th. Kauffmann*, Chimia *26*, 511 (1972).

[6] *Th. Kauffmann*, *A. Mitschker*, and *H.-J. Streitberger*, Angew. Chem. *84*, 829 (1972); Angew. Chem. internat. Edit. *11*, 847 (1972); *H. P. Mackowiak*, Diplomarbeit, Universität Münster 1974; *A. Mitschker*, Dissertation Universität Münster, probably 1974.

[7] *S. Gronowitz* and *H. O. Karlsson*, Ark. Kemi *17*, 89 (1960); *R. M. Kellogg*, *A. P. Schaap*, and *H. Wynberg*, J. Org. Chem. *34*, 343 (1969); *R. Hakansson*, Acta Chem. Scand. *25*, 1313 (1971).

[8] *S. Gronowitz*, Acta Chem. Scand. *15*, 1393 (1961).

[9] Cf. the analogous tetraphenylene synthesis: *G. Wittig* and *G. Klar*, Liebigs Ann. Chem. *704*, 91 (1967).

[10] *H.-J. Streitberger*, Dissertation, Universität Münster, probably 1974.

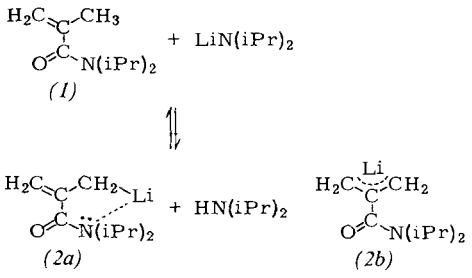
1,3-Anionic Cycloadditions of 2-(N,N-Diisopropylcarbamoyl)allyllithium with a Two-Step Mechanism[1][**]

By *Willi Bannwarth*, *Rudolf Eidenschink*, and *Thomas Kauffmann*[*]

Reaction of a solution of 1 mol of *N,N*-diisopropylmethacrylamide *(1)* (m.p. 47—47.5 °C) and 2 mol of *trans*-azobenzene in THF at −60 °C with 1 mol of lithium diisopropylamide affords 2-(*N,N*-diisopropylcarbamoyl)allyllithium *(2)* for which the structures *(2a)* and *(2b)* would appear most likely. The lithiation of *(1)* presumably proceeds at a temperature as low as −60 °C because hydrogen-metal exchange is promoted by the γ-N atom of the carboxamide group ("γ effect"[2]). Compound *(2)* adds to the azobenzene present, since workup of the reaction mixture after hydrolysis with water gave a 53% yield of 2-(1,2-diphenylhydrazinomethyl)-*N,N*-diisopropylacrylamide *(5)* (m.p. 110—111 °C). If the reaction is carried out at 65 °C, slow formation of the anionic cycloadduct *(4)* occurs *via* a route that can be shown[3] to involve the interme-

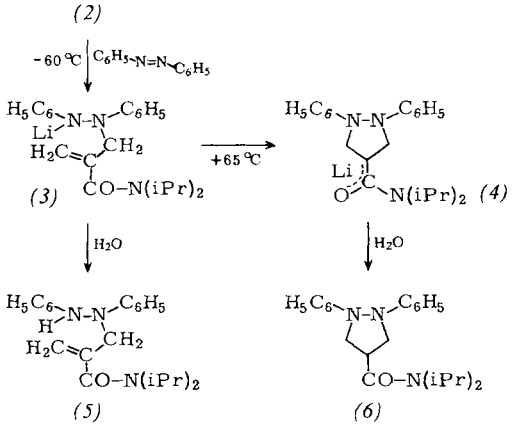
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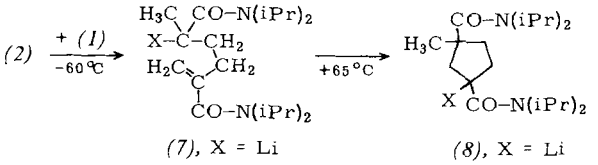
(1) *(2a)* *(2b)*

diate *(3)*. After addition of water, a 65% yield of *N,N*-diisopropyl-1,2-diphenylpyrazolidine-4-carboxamide *(6)* (m.p. 140 to 140.5 °C) could be obtained. The same product could be prepared by reaction of *(5)* with 1 mol of lithium diisopropylamide at 65 °C in THF and subsequent hydrolysis with water (92%).



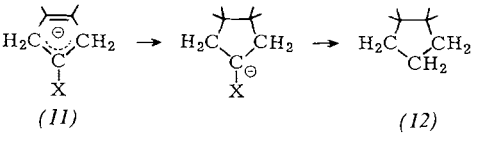
(2) *(3)* *(4)* *(5)* *(6)*

If the above reaction is carried out at −60 °C in the *absence of trans-azobenzene*, Michael addition of *(2)* to *(1)* affords the adduct *(7)*, for a 98% yield of bis(*N,N*-diisopropyl)-2-methyl-5-methylenehexanediamide *(9)* (oil purified by column chromatography; b.p. 135 °C/10 torr, $n_D^{20} = 1.4760$) was obtained after addition of water to the reaction mixture. The corresponding reaction at +65 °C leads—demonstrably *via* the open-chain adduct *(7)*[3]—to the anionic cycloadduct *(8)*, as shown by the isolation of bis(*N,N*-diisopropyl)-1-methylcyclopentane-1,3-dicarboxamide *(10)* (m.p. 114.5—116 °C) in 27% yield.



(7), X = Li *(8)*, X = Li
(9), X = H *(10)*, X = H

We have not yet accomplished cycloaddition of the lithium derivative *(2)* to olefins other than *(1)* to any significant extent. Compound *(2)*, which appears to be favored by having a relatively easily degradable auxiliary group —CON(*i*Pr)$_2$ permitting the cycloaddition process and bears no other substituents[4], therefore cannot be regarded as the reagent we are seeking in order to perform "cyclopentanation" of CC double bonds according to *(11)* → *(12)*. It may, however, represent a milestone on the way to this goal and may prove useful as a reagent in the synthesis of heterocycles.



(11) *(12)*

In the above reaction a 1,3-anionic cycloaddition has been shown for the first time to proceed in a stepwise, *i.e.* nonconcerted, manner.

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[1] 1,3-Anionic Cycloadditions, Part 12.—Part 11: *Th. Kauffmann*, Angew. Chem.; Angew. Chem. internat. Edit., in press.

[2] For the production of hydrogen-lithium exchange by a γ-N atom, cf. *e.g. R. L. Vaulx, W. H. Puterbaugh*, and *C. R. Hauser*, J. Org. Chem. *29*, 3514 (1964).

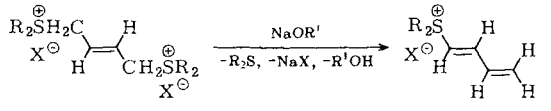
[3] Detected by TLC of samples removed at intervals from the reaction mixture.

[4] The allyl anions so far found to be capable of cycloaddition all contain difficultly degradable substituents: *R. Eidenschink* and *Th. Kauffmann*, Angew. Chem. *84*, 292 (1972); Angew. Chem. internat. Edit. *11*, 292 (1972); *G. Boche* and *D. Martens*, Angew. Chem. *84*, 768 (1972); Angew. Chem. internat. Edit. *11*, 724 (1972).

Butatrienylsulfonium Salts in Solution[**]

By *Heinz Braun, Gottfried Strobl*, and *Hannelore Gotzler*[*]

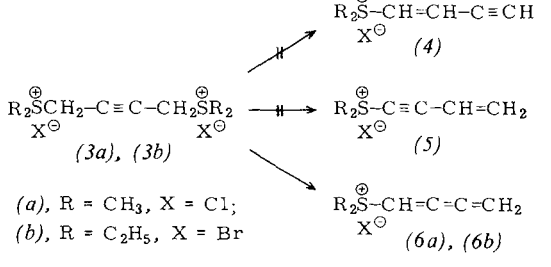
The *S,S,S',S'*-tetraalkyl-2-butenylenedisulfonium salts *(1)* react with equimolar amounts of alkali metal alkoxides in alcohol to give the crystalline butadienylsulfonium salts *(2)*[1].



(1a), *(1b)* *(2a)*, *(2b)*

(a), R = CH_3, X = Cl;
(b), R = C_2H_5, X = Br

We have investigated the corresponding reaction of the butynylenedisulfonium salts *(3)* which should afford butenynylsulfonium salts *(4)* and/or *(5)* and/or the butatrienylsulfonium salts *(6)* if it proceeds in analogous fashion.



(3a), *(3b)*

(a), R = CH_3, X = Cl;
(b), R = C_2H_5, X = Br

(4) *(5)* *(6a)*, *(6b)*

At room temperature, the reaction of *(3)* with alkoxides gives exclusively polymeric material. At −40 °C colorless solutions are formed (pH ≈ 7) which can be kept for several hours without any color change at −10 °C.

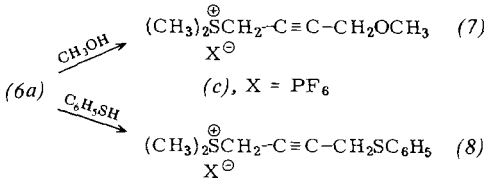
The ^{1}H-NMR spectrum (60 MHz, CD_3OH, −10 °C, TMS internal standard) of a solution prepared from *(3a)* and sodium trideuteriomethoxide [δ = 2.10 (s, 6H, dimethyl sulfide), δ = 3.18 (s, 6H, $(CH_3)_2S^+$), δ ≈ 6.3 (AB part of an ABX system, center of gravity, 2H), δ = 6.87 (X part of an ABX system, 1H); $J_{AX} + J_{BX} = 14.6$ Hz][2,3] indicated the structure

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(6a). The spectra of *(3a)*, *(2a)*, and chlorobutatriene[2] were used for comparison.

The ^{13}C-NMR spectrum confirmed the structural proposal, in particular on comparison with the spectrum of butatriene[4]. The UV spectrum [λ_{max}(ethanol) = 258 nm ($\varepsilon \geq 10^4$) also accords with the structure given. The spectra of butatriene[5] and *(2a)*, PF_6 instead of Cl[6], were used for comparison.



Reaction of the salts *(6)* with nucleophiles proceeds *via* 1,4-addition, formally yielding the monosubstitution products of the salts *(3)*. Cyclopentadiene affords propadienylsulfonium salts[7].

S,S-Dimethyl-S-(4-phenylthio-2-butynyl)sulfonium hexafluorophosphate (8c):

A solution of sodium (0.90 g, 0.039 mol) in anhydrous methanol (50 ml) is added dropwise to a stirred solution of *(3a)* (9.88 g, 0.04 mol) in anhydrous methanol (800 ml) at −40 °C over a period of 30 minutes. The colorless solution containing some unreacted *(3a)* shows pH ≈ 6.5.—Thiophenol (5.51 g, 0.05 mol) is then added and the reaction mixture is allowed to warm to room temperature within 3 hours. The solvent is distilled off and the solid residue is extracted with dichloromethane and freed from sodium chloride and traces of *(3a)* by filtration. Removal of the solvent and drying affords 9.80 g (95 %) of *S,S*-dimethyl-*S*-(4-phenylthio-2-butynyl)sulfonium chloride *(8a)*.—An aqueous solution of *(8a)* (1.00 g) is treated with a slight excess of ammonium hexafluorophosphate. Recrystallization of the precipitate from ethanol yields 1.20 g [80% based on *(3a)*] of colorless crystals decomposing in the range 52—53 °C.

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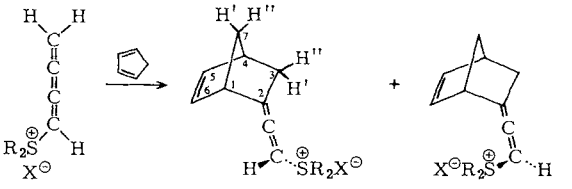
[1] *H. Braun, N. Mayer*, and *G. Kresze*, Liebigs Ann. Chem. *762*, 111 (1972).
[2] *R. Vestin, A. Borg*, and *T. Lindblom*, Acta Chem. Scand. *22*, 685 (1968).
[3] *M. L. Martin, F. Lefevre*, and *R. Mantione*, J. Chem. Soc. *B 1971*, 2049.
[4] *J. P. C. M. van Dongen, M. J. A. de Bie*, and *R. Steur*, Tetrahedron Lett. *1973*, 1371.
[5] *W. M. Schubert, T. H. Liddicoet*, and *W. A. Lanka*, J. Amer. Chem. Soc. *76*, 1929 (1954).
[6] *H. Braun* and *K. Fuckerieder*, unpublished.
[7] *H. Braun* and *G. Strobl*, Angew. Chem. *86*, 477 (1974); Angew. Chem. internat. Edit. *13*, 470 (1974).

Stable Propadienylsulfonium Salts by Cycloadditions with Butatrienylsulfonium Salts[**]

By *Heinz Braun* and *Gottfried Strobl*[*]

Propadienylsulfonium salts ("allenesulfonium salts") are accessible in equilibrium mixtures by isomerization of 2-propynylsulfonium salts and can be characterized by spectroscopy[1]. The salts undergo highly regiospecific addition with nucleophiles and are interesting intermediates[2, 3]. Propadienylsulfonium salts generated *in situ* have been proposed as reagents for peptide syntheses[1] and postulated as intermediates in fragmentations[4] and rearrangements[5, 6]. To our knowledge, no representative of this class has yet been isolated in pure form. In this communication we wish to report the preparation and characterization of stable propadienylsulfonium salts.

Whereas tetraarylbutatrienes add cyclopentadienones to the central double bond in Diels-Alder reactions[7], the terminal double bond acts as dienophilic component in diene syntheses of butatrienylsulfonium salts *(1)*[8] with cyclopentadiene.



(a), R = CH_3, X = Cl; *(c)*, R = CH_3, X = PF_6;
(b), R = C_2H_5, X = Br; *(d)*, R = C_2H_5, X = PF_6

[4+2] Cycloaddition of cyclopentadiene and *(1)* affords mixtures of the crystalline salts *(2)* (≈ 50 %) and *(3)* (≈ 50 %) in yields of about 90 %.

(2a)/(3a) and *(2b)/(3b)* are soluble in water, alcohols, and chloroform, and can be recrystallized from ethanol/ether. *(2c)/(3c)* (dec. 140—150 °C) and *(2d)/(3d)* (dec. 80—85 °C) are stable at room temperature and yield correct analytical data. Structural assignment of *(2a)/(3a)* is based on the following findings:

1) ^{1}H-NMR spectrum (60 MHz, $CDCl_3$, TMS internal standard): δ = 7.3—7.1 (m, $^+$S—CH=), 6.5—6.0 (m, 5-H + 6-H), 3.6 (mc, 1-H), 3.45 (s) and 3.37 (s, total of 6H, $(CH_3)_2S^+$ of *(2a)* and *(3a)*, respectively), 3.2 (mc, 4-H), 2.7 (mc, 3-H''), 2.1 (mc, 3-H'), 1.6 (mc, 7-H' + 7-H''). Only the signals of the dimethylsulfonio groups can be evaluated separately for *(2a)* and *(3a)*, the other signals of corresponding protons of *(2a)* and *(3a)* appear together in the spectrum of the mixture.

2) UV spectrum (ethanol): Continuous absorption in the range 35000—50000 cm^{-1} with a maximum at 50000 cm^{-1} ($\varepsilon = 3.7 \times 10^4$) preceded by a shoulder at 40000 cm^{-1} ($\varepsilon = 3 \times 10^3$).

3) IR spectrum (KBr): 1960 ($\nu_{C=C=C}$), 1625 cm^{-1} ($\nu_{C=C}$). No absorption in the region 2260—2100 cm^{-1} ($\nu_{C\equiv C}$).

4) The ^{13}C-NMR spectrum confirms the proposed structure (see also ref.[9]). The appearance of separate signals for *(2a)* and *(3a)* demonstrates that both diastereoisomers were formed.

(RS)- and (SR)-S,S-Dimethyl-S-2-(5-norbornen-2-ylidene)-vinylsulfonium chloride (2a) and (3a)

A 1.5 M solution of sodium methoxide (57 ml) is added dropwise to a stirred suspension of *S,S,S',S'*-tetramethyl-2-butynylenedisulfonium chloride[8] (22.2 g, 0.09 mol) in anhydrous methanol (700 ml) at −40 °C over a period of 2 hours. After addition of cyclopentadiene (33.0 g, 0.5 mol) and 15 hours' stirring at −40 °C, the reaction mixture is warmed to room temperature within 8 h. The solvent is distilled off (rotary evaporator, bath temp. 30—40 °C) and the residue extracted with chloroform and freed from sodium chloride by filtration. Removal of the solvent and drying (25 °C at 0.1 torr) afforded 17.5 g (95 %) of a mixture of *(2a)* and *(3a)* which was shown to be pure by NMR spectroscopy. Recrystallization from

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anhydrous ethanol/ether gave colorless crystals decomposing in the range 110—115 °C.

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[1] *G. D. Appleyard* and *C. J. M. Stirling*, J. Chem. Soc. *C 1969*, 1904.
[2] *J. W. Batty*, *P. D. Howes*, and *C. J. M. Stirling*, J. C. S. Perkin I *1973*, 59.
[3] *J. W. Batty*, *P. D. Howes*, and *C. J. M. Stirling*, J. C. S. Perkin I *1973*, 65.
[4] *A. Terada* and *Y. Kishida*, Chem. Pharm. Bull. *17*, 974 (1969).
[5] *L. Veniard* and *G. Pourcelot*, C. R. Acad. Sci. *C 273*, 1190 (1971).
[6] *A. Terada* and *Y. Kishida*, Chem. Pharm. Bull. *18*, 490 (1970).
[7] *W. Ried* and *R. Neidhardt*, Liebigs Ann. Chem. *739*, 155 (1970).
[8] *H. Braun*, *G. Strobl*, and *H. Gotzler*, Angew. Chem. *86*, 477 (1974); Angew. Chem. internat. Edit. *13*, 469 (1974).
[9] *J. K. Crandall* and *S. A. Sojka*, J. Amer. Chem. Soc. *94*, 5084 (1972), and references cited therein.

dium acetate and 2,4-pentanedione (for conditions see Table 1).

Compound *(1)* which was isolated by fractional distillation crystallizes as white leaflets (from ethanol), m.p. 62—64 °C (64 °C[3]). Elemental analysis, mass spectrum, and ^{1}H-NMR spectrum are in accord with the structure given. The dimers *(2)* were isolated from the oily fraction (b.p. 125 to 150 °C/0.5 torr) by chromatography (alumina, hexane/benzene, 1 : 1). The gas chromatogram displays three isomers; a molecular peak is observed in the mass spectrum.

Dibenzofuran is known to be formed as a by-product in poor yield when diphenyl ether is heated to 700 °C in a glass

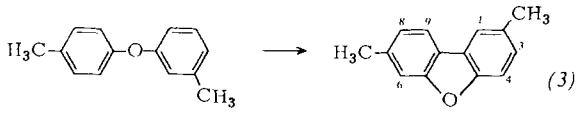

(3)

Table 1. Products of intramolecular ring-closure reactions and dimers (determined by gas chromatography). Reaction conditions: starting material, 15.0 g; $Pd(OAc)_2$, 0.15 mmol; 2,4-pentanedione 0.15 mmol; N_2/O_2 (1 : 1) 50 kg/cm^2; 5 h at 150 °C (yield based on reacted palladium acetate).

Starting material	Cyclized product	Yield [mol-%]	Dimerized products yield [mol-%]
Diphenyl ether	Dibenzofuran	8090	3710
Diphenyl ether [a]	Dibenzofuran	10400	2530
Di-*p*-tolyl ether	2,8-Dimethyldibenzofuran	8540	1470
Di-*p*-tolyl ether [b]	2,8-Dimethyldibenzofuran	9360	1310
m-Tolyl *p*-tolyl ether	2,7-Dimethyldibenzofuran	730	330
m-Tolyl *p*-tolyl ether [b]	2,7-Dimethyldibenzofuran	1530	680
m-Tolyl *p*-tolyl ether [a]	2,7-Dimethyldibenzofuran	9220	590
o-Tolyl *p*-tolyl ether [a]	2,6-Dimethyldibenzofuran	330	110
4-Nitrodiphenyl ether [a]	2-Nitrodibenzofuran [d]	5230	traces
Benzophenone [a]	Fluorenone	650	690
4,4'-Dimethylbenzophenone [a, c]	3,6-Dimethylfluorenone	1120	traces

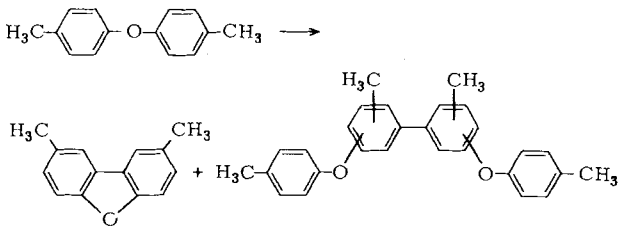
[a] With addition of ethylene diacetate (5 ml).
[b] With addition of mesitylene (5 ml).
[c] At 180 °C; the reaction gave a very poor yield at 150 °C.
[d] Yellow needles, m.p. 150—151 °C (150.5—151.5 °C [7]), molecular ion at *m/e* 213.

Dibenzofurans by Intramolecular Ring Closure Reactions

By *Akinori Shiotani* and *Hiroshi Itatani*[*]

Palladium compounds are very important in the homogeneous catalysis of organic reactions[1]. The oxidative coupling reactions of aromatic compounds were investigated in the presence of palladium acetate under oxygen pressure. The dimerized compounds were obtained in good yield in the absence of solvent[2].

We have now accomplished an intramolecular ring-closure reaction to give 2,8-dimethyldibenzofuran *(1)* in the corresponding reaction of di-*p*-tolyl ether in the presence of palladium acetate and 2,4-pentanedione (for conditions see Table 1).


(1) *(2)*

Compound *(1)* which was isolated by fractional distillation crystallizes as white leaflets (from ethanol), m.p. 62—64 °C (64 °C[3]). Elemental analysis, mass spectrum, and ^{1}H-NMR spectrum are in accord with the structure given. The dimers *(2)* were isolated from the oily fraction (b.p. 125 to 150 °C/0.5 torr) by chromatography (alumina, hexane/benzene, 1 : 1). The gas chromatogram displays three isomers; a molecular peak is observed in the mass spectrum.

Dibenzofuran is known to be formed as a by-product in poor yield when diphenyl ether is heated to 700 °C in a glass tube[4]. The method developed by us is suitable for the preparation of substituted dibenzofurans (see Table 1) which have hitherto only been accessible by laborious multistep syntheses[5]. Substituents on the benzene nucleus favor intramolecular ring closure and suppress dimerization owing to the reduced interaction between the molecules. Solvents have the same effect[6].

The analogous reaction of *m*-tolyl *p*-tolyl ether gave white needles (m.p. 82—83 °C). Elemental analysis and mass spectrum are in accord with the expected structure of a 2,7- or 2,9-dimethyldibenzofuran; the ^{1}H-NMR spectrum showed 2,7-dimethyldibenzofuran *(3)* to be present [(in CCl_4): $\delta = 2.47$ (2 CH_3), 7.02 (H^8), 7.10 (H^3), 7.28 (H^6), 7.35 (H^4), 7.60 (H^1), 7.67 (H^9); $J_{1,3} = 1.5$ Hz, $J_{3,4} = 7.5$ Hz, $J_{1,4} \approx 0.6$ Hz, $J_{6,8} = 1.2$ Hz, $J_{8,9} = 7.5$ Hz, $J_{6,9} \approx 0.5$ Hz].

In the same way, fluorenones are formed from benzophenones, although in low yields (see Table 1). Diphenyl sulfide, diphenyl sulfone, *N,N*-diphenylacetamide, and phenyl benzoate could not be reacted.

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[1] a) *R. Hüttel*, Synthesis *1970*, 225; b) *P. M. Maitlis*: The Organic Chemistry of Palladium. Vol. 1 and 2. Academic Press, New York 1971.
[2] *H. Itatani* and *H. Yoshimoto*, J. Org. Chem. *38*, 76 (1973); Bull. Chem. Soc. Jap. *46*, 2490 (1973).
[3] *Y. Sugii* and *H. Shindo*, J. Pharm. Soc. Jap. *53*, 97 (1933).
[4] *R. Nakai*, Bull. Chem. Soc. Jap. 5, 136 (1930).

[5] a) *W. E. Parham* and *R. W. Strassburg*, J. Org. Chem. 26, 4749 (1961); b) *D. F. DeTar* and *T. E. Whiteley*, J. Amer. Chem. Soc. 79, 2498 (1957).

[6] The solvent should not undergo dimerization.

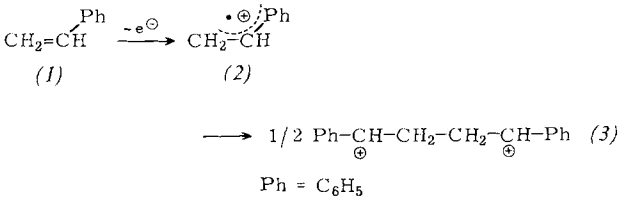
[7] *M. J. S. Dewar* and *D. S. Urch*, J. Chem. Soc. *1957*, 345.

Hydroxylating Dimerization of Styrene at the Anode[1][**]

By *Eberhard Steckhan* and *Hans Schäfer*[*]

The dimerization and functionalization of electron-rich olefins at the graphite anode has hitherto been performed mainly in methanolic solution. The process yields predominantly 1,4-dimethoxylated butane derivatives in good yields[2].

We are currently investigating the introduction of other functional groups by variation of the nucleophile. Electrolysis in aqueous electrolytes should lead to the formation of substituted 1,4-butanediols and tetrahydrofurans.

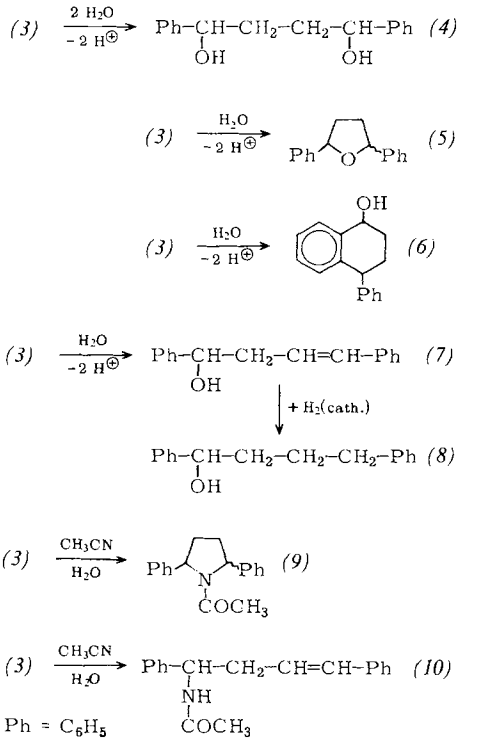


(1) *(2)*

$\longrightarrow$ 1/2 Ph–CH(⊕)–CH_2–CH_2–CH(⊕)–Ph *(3)*

Ph = C_6H_5

The potential-controlled preparative electrolysis of styrene *(1)* ($E = +1.2$ to $+1.6$ V relative to Ag/AgCl) at graphite electrodes affords the products *(4)* to *(10)* in aqueous acetonitrile or a dichloromethane/water suspension (Table 1). Their formation is readily interpreted as proceeding *via* the intermediate dication *(3)* and its deprotonation or solvolysis.



(3) $\xrightarrow[-2\,H^{\oplus}]{2\,H_2O}$ Ph–CH(OH)–CH_2–CH_2–CH(OH)–Ph *(4)*

(3) $\xrightarrow[-2\,H^{\oplus}]{H_2O}$ 2,5-Diphenyltetrahydrofuran *(5)*

(3) $\xrightarrow[-2\,H^{\oplus}]{H_2O}$ 1-Phenyl-1,2-dihydronaphthalen-1-ol *(6)*

(3) $\xrightarrow[-2\,H^{\oplus}]{H_2O}$ Ph–CH(OH)–CH_2–CH=CH–Ph *(7)*

$\downarrow$ + H_2(cath.)

Ph–CH(OH)–CH_2–CH_2–CH_2–Ph *(8)*

(3) $\xrightarrow[H_2O]{CH_3CN}$ 1-Acetyl-2,5-diphenylpyrrolidine *(9)*

(3) $\xrightarrow[H_2O]{CH_3CN}$ Ph–CH(NH–$COCH_3$)–CH_2–CH=CH–Ph *(10)*

Ph = C_6H_5

of +1.6 V (relative to Ag/AgCl), and a current density of 25 mA/cm² until consumption of 0.1 F. After extraction of the electrolyte with ether and dichloromethane and distillation of the solvent and unreacted styrene there remains 19 g of crude product. The crude product still contains small amounts of olefin and supporting electrolyte. 2.35 g was separated by column chromatography over silica gel (270 g; eluant: light petroleum/ether 3:1, v/v). Compound *(5)* (720 mg), b.p. 190 to 193 °C/12 torr, was eluted as the second fraction.

Table 1. Results of hydroxylating anodic dimerization of styrene in aqueous electrolytes. The compounds *(4)* to *(10)* were characterized by C,H analysis and/or their IR, NMR, and mass spectra, as well as comparison with authentic samples. Conditions: Electrolysis was performed at a potential of +1.2 to +1.6 V relative to Ag/AgCl and a current density between 20 and 30 mA/cm² up to a conversion of 0.1 F.

Products	Electrolyte		
	CH_3CN/styrene/H_2O = 5:2:1 (v/v/v), TEA—*p*TS [a] (0.6 M)	CH_3CN/styrene/H_2O = 5:2:1 (v/v/v), TBA—HSO_4 [a] (0.4 M)	CH_2Cl_2/styrene/H_2O [b] = 5:2:1 (v/v/v), TBA—HSO_4 [a] (0.5 M)
	yield % [c]	yield % [c]	yield % [c]
(4)	8.5	14	1.5
(5)	38	40	52
(6)	4	9	1 (14) [d]
(7)	—	—	2.6
(8)	—	—	5.5
(9)	12	12	—
(10)	3.5	4	—

[a] TEA—*p*TS = tetraethylammonium *p*-toluenesulfonate; TBA—HSO_4 = tetrabutylammonium hydrogen sulfate.
[b] In CH_2Cl_2/styrene/H_2O = 6:2:1 (v/v/v) TEA-*p*TS (0.56 M) styrene telomers and polymers are mainly formed. The anode is strongly passivated. However, in the electrolytes used here no passivation is observed.
[c] Based on the current consumption.
[d] Plus 14% of dehydrated *(6)*, *i.e.* 1-phenyl-1,2-dihydronaphthalene.

2,5-Diphenyltetrahydrofuran (5)[3]

A sample of styrene (40 ml) in an electrolyte consisting of dichloromethane (100 ml), water (20 ml), and tetrabutylammonium hydrogen sulfate (30 g) is electrolyzed at graphite electrodes (P 127, Sigri, Meitingen) at 25 °C, an anode potential

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[1] Presented in part at the XXIVth IUPAC Congress, Hamburg, September 1973.—Anodic Oxidation of Organic Compounds, Part 12.—Part 11: *D. Koch* and *H. Schäfer*, Angew. Chem. 85, 264 (1973); Angew. Chem. internat. Edit. 12, 245 (1973).

[2] *H. Schäfer* and *E. Steckhan*, Angew. Chem. 81, 532 (1969); Angew. Chem. internat. Edit. 8, 518 (1969); *H. Schäfer*, Chem.-Ing.-Tech. 42, 164 (1970);

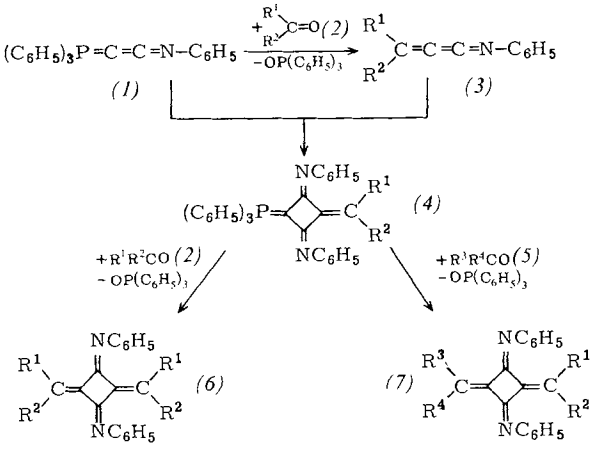
H. Schäfer and *E. Steckhan*, *ibid.* *44*, 186 (1972); Tetrahedron Lett. *1970*, 3835.

[3] Tetrahydrofuran derivatives represent starting compounds for the synthesis of a variety of interesting compounds: *W. Reppe et al.*, Liebigs Ann. Chem. *596*, 86 (1955).

Reaction of *N*-Phenyl(keteniminylidene)triphenylphosphorane with Carbonyl Compounds

By *Hans Jürgen Bestmann* and *Günter Schmid*[*]

The reaction of *N*-phenyl(keteniminylidene)triphenylphosphorane *(1)*[1] with aromatic aldehydes *(2)*, $R^1 = Ar$, $R^2 = H$, in a molar ratio of 1:1 yields the hitherto unknown, deeply colored 1,3-bis(arylmethylene)-2,4-bis(phenylimino)cyclobutanes *(6)*, $R^1 = Ar$, $R^2 = H$.



It can only be assumed that a Wittig reaction between *(1)* and *(2)* initially gives the arylmethyleneketenimines *(3)*, $R^1 = Ar$, $R^2 = H$, which immediately undergo cycloaddition with *(1)* to form the ylides *(4)*, which themselves react with a second molecule of *(2)* affording *(6)*. After reaction between *(1)* and *(2)* in the molar ratio 2:1, the phosphoranes *(4)* can often be isolated in crystalline form or reacted in the product solution with another carbonyl compound *(5)* to yield *(7)* (Table 1).

molecular-spectroscopic data and elemental analysis were obtained for all the compounds listed in Table 1.

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[1] *H. J. Bestmann* and *G. Schmid*, Angew. Chem. *86*, 274 (1974); Angew. Chem. internat. Edit. *13*, 273 (1974).

Model Experiments for Peptide Fragment Coupling without Racemization-Prone Activated Amino Acid Derivatives

By *Hasso von Zychlinski*, *Ivar Ugi*, and *Dieter Marquarding*[*]

The fragment strategy is one of the most useful synthetic concepts for peptides and proteins[1]. This involves the stepwise synthesis of peptide fragments with two or more amino acid units, and subsequent coupling of fragments by acylation. Since the latter requires the activation of the C-terminal amino acid unit of a peptide fragment, there is substantial danger of racemization *via* the azlactone which can be formed from the activated intermediate. Even the azide method has recently been shown not to be free from racemization[2, 3]. It is not yet possible to assess whether *Kemp*'s reagent[4] or the combination of dicyclohexylcarbodiimide and *N*-hydroxysuccinimide[5] generally affords racemization-free coupling of peptide fragments.

All coupling methods which are based upon the conventional concept of peptide bond formation by acylation proceed as second order reactions, whereas the concurrent racemization processes correspond to first or pseudo first order kinetics. Accordingly, it can by no means be taken for granted that a method which leads to a negligible degree of racemization in the case of small peptides and relatively high concentrations of reactants will be equally good with larger fragments. However, in fragment coupling by four-component condensation[6] of an N-terminally and a C-terminally protected peptide fragment *(1)* and *(2)* with an isocyanide *(3)* and an aldehyde *(4)*, racemization-prone activated peptide derivatives of conventional type are avoided; formation of the new peptide bond occurs by a first order reaction. The only intermediate which could lead to racemization is *(5)*, but it rearranges spontaneously and immeasurably fast into the stable product *(6)*[6].

The usefulness of such a sequence of reactions as a method of fragment coupling depends in a critical manner upon the cleavage *(6)*→*(7)* which must be accomplished without

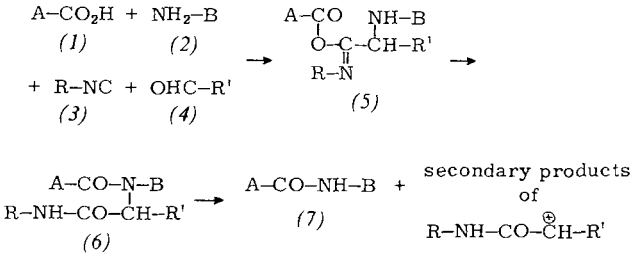
Table 1. Products of type *(4)*, *(6)*, and *(7)*.

	R^1	R^2	R^3	R^4	*(4)*, M.p. [°C] (yield [%]), color	*(6)* or *(7)*, M.p. [°C] (yield [%]), color
a	*p*-NO_2—C_6H_4	H			245 (64), orange-red	245 (65), black-red
b	*p*-CH_3—C_6H_4	H				239 (36), red
c	*p*-CH_3—C_6H_4	H	*p*-NO_2—C_6H_4	H		221 (40), red-violet
d	α-$C_{10}H_7$	H				248 (59), red
e	α-$C_{10}H_7$	H	*p*-NO_2—C_6H_4	H		218 (35), red-violet
f	C_6H_5	C(=O)—C_6H_5			232 (58), yellow	
g	—*o*-C_6H_4—*o*-C_6H_4—				247 (75), red	

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decomposition or racemization of the final product *(7)*. This is only possible if group R' of the aldehyde *(4)* assists the cleavage reaction[7].



We found in model four-component condensations with phenylacetic acid *(1a)*, benzylamine *(2a)*, *tert*-butyl isocyanide, and the aldehydes *(4a)*—*(4d)* that the condensation products *(6)*, $A=B=C_6H_5CH_2$, $R=t\text{-}C_4H_9$ could be cleaved with cold trifluoroacetic acid to yield *N*-(benzyl)phenylacetamide, *(7)*, $A=B=C_6H_5CH_2$ (Table 1).

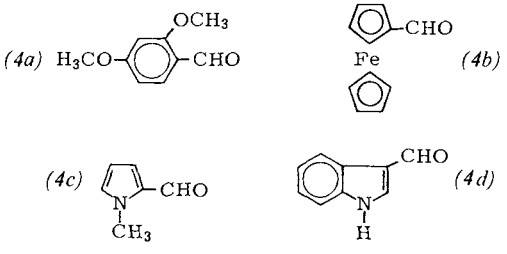
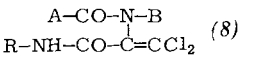


Table 1. Results of model four-component condensations of *(1a)*, *(2a)*, *(3a)* and the aldehydes *(4a)*—*(4d)* (reaction conditions: 20 mmol of each reactant in 30—50 ml of methanol, THF, or dichloromethane at 0—20 °C). The products *(6)*, $A=B=C_6H_5CH_2$, $R=t\text{-}C_4H_9$, were cleaved with cold trifluoroacetic acid to form *(7)*, $A=B=C_6H_5CH_2$.

Aldehyde	*(6)* Yield [%]	m.p. [°C]	*(6)*→*(7)* T [°C]	t [h]	Yield [%]
(4a)	75	167—168	0	20	23
			40	4	38
(4b)	77	175—176	0	20	49
(4c)	68	146—148	20	2	53
			20	4	63
(4d)	62	216—219	20	4	63
			20	18	70

We found also that chloral leads to products of type *(6)* which cannot be isolated [*e.g.* *(6)*, $A=B=C_6H_5CH_2$, $R'=CCl_3$, $R=t\text{-}C_4H_9$] because of their spontaneous decomposition into *(7)* (43—49%), presumably *via* the intermediate *(8)*.



A product of type *(6)*, $A=B=C_6H_5CH_2$, $R=c\text{-}C_6H_{11}$, $R'=2\text{-}NO_2\text{—}C_6H_4$ (72%, m.p. 213—215 °C) is obtained by four-component condensation from *o*-nitrobenzaldehyde. In analogy to the *o*-nitrobenzylurethanes[9], it is photolyzed to form *(7)*, $A=B=C_6H_5CH_2$ (65%).

Model four-component condensations and cleavage experiments with *N*-acylated amino acids and peptides *(1)*, in combination with C-terminally protected amino acid derivatives *(2)* are presently being carried out in order to determine if and under which conditions these peptide coupling reactions proceed without racemization[10].

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[1] Review: *E. Wünsch*, Angew. Chem. *83*, 773 (1971); Angew. Chem. internat. Edit. *10*, 786 (1971).

[2] *D. S. Kemp* and *S. W. Wang*, J. Amer. Chem. Soc. *92*, 1053, 4756 (1970); see also *D. S. Kemp* and *J. Rebek*, *ibid.* *92*, 5792 (1970).

[3] *L. Kisfaludy* and *D. Nyeki*, Acta Chim. Acad. Sci. Hung. *72*, 75 (1972).

[4] *D. S. Kemp* and *S. W. Chien*, J. Amer. Chem. Soc. *89*, 2743 (1967); see also *D. S. Kemp* and *R. B. Woodward*, Tetrahedron *21*, 3019 (1965).

[5] *F. Weygand* and *U. Ragnarsson*, Z. Naturforsch. *21b*, 1141 (1966); *E. Wünsch*, *ibid.* *22b*, 1269 (1967); see also *G. V. Anderson*, *J. E. Zimmermann*, and *F. M. Callahan*, J. Amer. Chem. Soc. *85*, 3039 (1963); *86*, 1839 (1964); *K. Hofmann*, *ibid.* *87*, 631 (1965).

[6] Review: *I. Ugi*, Intra-Sci. Chem. Rep. *5*, 229 (1971); see also: Isonitrile Chemistry. Academic Press, New York 1971, Chapters 8 and 9, and literature quoted therein.

[7] The 2,4-dimethoxybenzyl, and the 2,4,6-trimethoxybenzyl groups can be removed from the amide nitrogen atom by treatment with trifluoroacetic acid [8].

[8] *F. Weygand*, *W. Steglich*, and *J. Bjarnason*, Chem. Ber. *101*, 3642 (1968), and preceding communications.

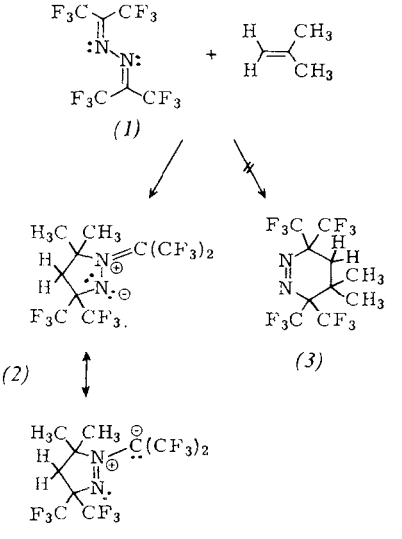
[9] *R. B. Woodward* and *A. Patchornik*, J. Amer. Chem. Soc. *92*, 6333 (1970).

[10] Note (May 7, 1974): In the meantime analogous reactions have been used for the synthesis of dipeptides (*H.-S. Nah*, Ph. D. Thesis, University of Southern California, 1973) and of tripeptides (unpublished work by *L. Wackerle* at our Institute). According to antipode analyses by *E. Gil-Av* and *B. Feibush* (Weizmann Institute, Rehovot, Israel) and *U. Ragnarsson* (University of Uppsala, Sweden) no racemization is observed if drastic reaction conditions are avoided. [*E. Gil-Av*, *B. Feibush*, *D. Marquarding*, *H.-S. Nah*, *U. Ragnarsson*, *I. Ugi*, *L. Wackerle*, and *H. v. Zychlinski*, publication in preparation].

The 1:1 Intermediate of the "Criss-Cross" Cycloaddition of Isobutylene to Hexafluoroacetone Azine[1][***]

By *Klaus Burger* and *Willy Thenn*[*], together with *Alfred Gieren*[**]

Hexafluoroacetone azine *(1)*[2, 3] reacts with electron-rich olefins to form "criss-cross" cycloadducts (1,3-:2,4-addition)[4] such as 1,5-diazabicyclo[3.3.0]octanes. The 1:1 intermediate



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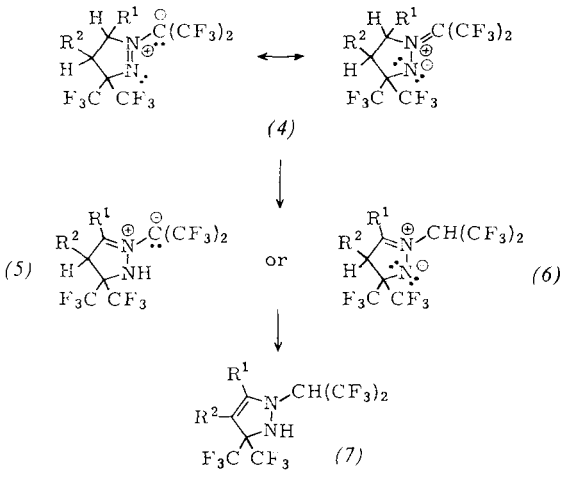
[***] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

of the reaction of *(1)* with isobutylene has recently been isolated and assigned the structure of a Diels-Alder adduct *(3)*[5]. However, the proposed structure and the mechanistic interpretations derived therefrom are incorrect. Isobutylene reacts with equimolar amounts of *(1)* on two-days' shaking at room temperature in a sealed tube to give *(2)* which still contains some 2:1 adduct. Separation is feasible by crystallization. The amount of "criss-cross" cycloadduct increases with increasing reaction temperature.

The proposed structure *(3)*[5] is inconsistent with the ^{19}F-NMR spectrum ($CDCl_3$, CF_3COOH as external standard), which contains three signals at -5.1, -12.5, and -26.0 ppm in the ratio 2:1:1, and with mass spectral decomposition (no elimination of N_2), the ^{13}C-NMR spectrum[6], and the reactions[7, 8].

We found that the 1:1 adduct is a stable azomethinimine[9], 2-[5,5-dimethyl-3,3-bis(trifluoromethyl)-1H^+-1-pyrazolinio]-1,1,1,3,3,3-hexafluoro-2-propanide. The structure of *(2)* was proved unequivocally by X-ray structure analysis[10]. This constitutes the first isolation and characterization of the 1,3-dipolar intermediate of "criss-cross" cycloaddition postulated by *Huisgen*[11].

An azomethinimine intermediate *(4)* also readily explains the reaction of *(1)* with cyclopentene and olefins of the type $CHR^1{=}CHR^2$ (R^1 = isopropyl or *tert*-butyl, R^2 = H) to give 3-pyrazolines *(7)*.



A series of intramolecular de- and reprotonations *via* intermediates such as *(5)* and *(6)* provide a plausible mechanistic interpretation. If the final step of the rearrangement were to be a [1.4]-sigmatropic H shift[12], then *(6)* would be expected as sole intermediate.

2-[5,5-Dimethyl-3,3-bis(trifluoromethyl)-1H^+-1-pyrazolinio]-1,1,1,3,3,3-hexafluoro-2-propanide (2)

Isobutylene (2.80 g, 50 mmol) and compound *(1)*[2, 3] (16.40 g, 50 mmol) are shaken together at room temperature in a sealed tube for 2 to 3 days. The resulting crystals are recrystallized from anhydrous hexane; yield 16.35 g (85%) of *(2)*, m.p. 77—78 °C.

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[1] Reactions with Hexafluoroacetone Azine, Part 2.—Part 1: *K. Burger, W. Thenn, J. Fehn, A. Gieren,* and *P. Narayanan,* Chem. Ber. *107,* 1526 (1974).

[2] *W. J. Middleton* and *C. G. Krespan,* J. Org. Chem. *30,* 1398 (1965).

[3] *K. Burger, J. Fehn,* and *W. Thenn,* Angew. Chem. *85,* 541 (1973); Angew. Chem. internat. Edit. *12,* 502 (1973).

[4] *T. P. Forshaw* and *A. E. Tipping,* J. Chem. Soc. *C 1971,* 2404.

[5] *S. E. Armstrong* and *A. E. Tipping,* J. Fluorine Chem. *3,* 119 (1973).

[6] *J. Firl, K. Burger,* and *W. Thenn,* to be published.

[7] *K. Burger, W. Thenn, H. Schickaneder,* and *H. Peuker,* Angew. Chem. *86,* 483 (1974); Angew. Chem. internat. Edit. *13,* 476 (1974).

[8] *K. Burger, W. Thenn, R. Rauh,* and *H. Schickaneder,* Angew. Chem. *86,* 484 (1974); Angew. Chem. internat. Edit. *13,* 477 (1974).

[9] For stable azomethinimines see: *R. Huisgen, R. Fleischmann,* and *A. Eckell,* Tetrahedron Lett. *1960,* (12) 1; *R. Huisgen* and *A. Eckell, ibid. 1960,* (12) 5; *H. Dorn* and *A. Otto,* Chem. Ber. *101,* 3287 (1968), and references given therein.

[10] *A. Gieren* and *P. Narayanan,* and *K. Burger* and *W. Thenn,* Angew. Chem. *86,* 482 (1974); Angew. Chem. internat. Edit. *13,* 475 (1974).

[11] *R. Huisgen,* Angew. Chem. *75,* 604 (1963); Angew. Chem. internat. Edit. *2,* 565 (1963).

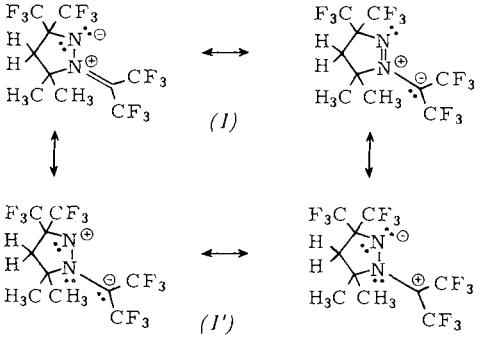
[12] *P. Gruber, L. Müller,* and *W. Steglich,* Chem. Ber. *106,* 2863 (1973), and references given therein.

X-Ray Structure Analysis of the 1:1 Intermediate of the "Criss-Cross" Cycloaddition of Isobutylene to Hexafluoroacetone Azine

By *Alfred Gieren* and *Poojappan Narayanan*[*], together with *Klaus Burger* and *Willy Thenn*[**]

The 1:2 "criss-cross" cycloaddition[1] of hexafluoroacetone azine[2, 3] to isobutylene proceeds *via* a 1:1 intermediate[4, 5]. X-Ray structure analysis shows unequivocally that the stable azomethinimine 2-[5,5-dimethyl-3,3-bis(trifluoromethyl)-1H^+-1-pyrazolinio]-1,1,1,3,3,3-hexafluoro-2-propanide *(1)* is formed, thus confirming *Huisgen's* postulate of a 1,3-dipolar intermediate of the "criss-cross" cycloaddition[6].

Monoclinic single crystals of *(1)* were obtained from hexane solution. Space group: $P2_1/a$; $a = 12.67_8$, $b = 11.38_8$, $c = 9.98_6$ Å, $\gamma = 106.4_5°$; $d_{exp} = 1.82\,g\cdot cm^{-3}$; 4 molecules per unit cell; $d_{calc} = 1.84\,g\cdot cm^{-3}$. 2623 independent reflections (403 not observed, $I \leq 2\sigma_I$; $\vartheta/2\vartheta$ scan, five-point measurement, $\vartheta \leq 70°$) were measured with an automatic single crystal diffractometer using $Cu_{K\alpha}$ radiation. The structure was solved with the aid of the direct method program PHASDT[7].

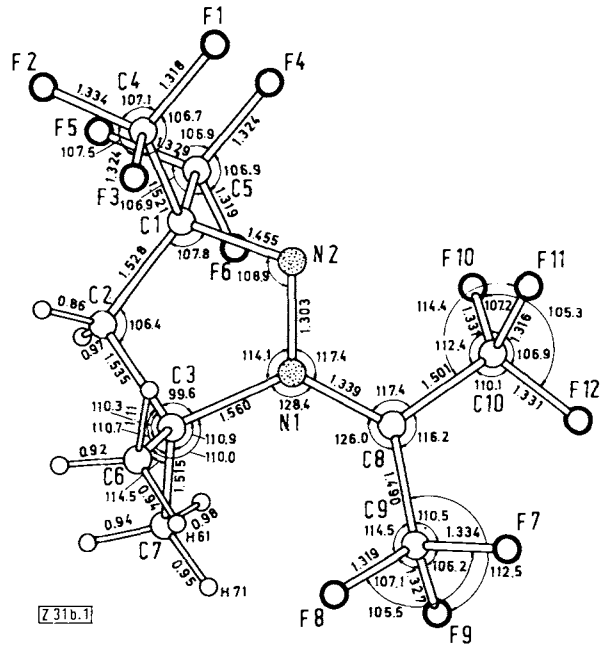


All the atoms (except H) were visible in an *E*-Fourier synthesis with 299 phased reflections. Least-squares refinement, first with isotropic and then with anisotropic temperature factors, was performed up to an *R* factor of 8.7% (observed reflections). A difference Fourier synthesis calculated at this stage showed all the H atoms. Upon inclusion of the H atoms in the refinement, convergence was obtained at $R = 4.4\%$.

The structure of the molecule is shown in Figure 1. The N1—N2 and C8—N1 distances indicate strong double bond components of approximately equal magnitude. The zwitterionic compound is therefore essentially described by the two resonance formulas *(1)*. The mean value of the C—C(sp^3—sp^3)

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C4—C1—N2:	107.2°	C5—C1—N2:	107.1
C4—C1—C2:	113.0°	C5—C1—C2:	110.1
C1—C4—F1:	113.2°	C1—C5—F4:	113.3
C1—C4—F2:	111.5°	C1—C5—F5:	112.3
C1—C4—F3:	110.6°	C1—C5—F6:	110.2°

C4—C1—C5: 111.4°

C1—C5:	1.519 Å	C3—C6:	1.521 Å

Fig. 1. Molecular structure of 2-[5,5-dimethyl-3,3-bis(trifluoromethyl)-1*H*$^+$-1-pyrazolinio]-1,1,1,3,3,3-hexafluoro-2-propanide *(1)*. The mean standard deviations of the given bond lengths and angles amount to: 0.004 Å (except C—H: 0.04 Å) and 0.3 respectively.

bond lengths in the five-membered ring amounts to 1.532 Å, and that of the exocyclic C—C(sp^3—sp^3) bonds is 1.519 Å. Expectedly, the sp^2—sp^3 type bonds originating from C8 (to C9 and C10) are somewhat shorter. The mean value of the C—F bond lengths is 1.326 Å. Like these bond lengths, the C1—N2(sp^3—sp^2) bond also corresponds to the expected value. However, the isotypic C3—N1 bond shows an exceptional degree of lengthening (more than 0.1 Å, see below).

The geometry of the compound reflects the high degree of substitution of the five-membered ring. Thus the elongation of the C3—N1 bond arises because of the strain in the $C6H_3(C7H_3)$—C3—N1—C8—$C9F_3$ system due to the methyl groups on C3 and the $C9F_3$ group. The intramolecular contacts F8···H61 and F8···H71 are only 2.15 and 2.28 (±0.04) Å respectively. Repulsion between the two methyl groups and the $C9F_3$ group is also responsible for the opening of the angles at N1 and C8 lying within this system. Typically, the angles facing the lone pair (on N2) are reduced[8].—This effect is also observed for the angles at C1. The intramolecular interactions also lead to twisting about the N1—C8 bond which displays double bond character: C9—C8—N1—C3: −24.4° and C10—C8—N1—N2: −13.3°. The difference in twisting about the C8—N1 bond causes the sp^2 carbon atom C8 to project out of the plane of its three neighboring atoms by 0.05 Å. N1 is also displaced to some extent from the plane of its three neighbors (Δ = 0.02 Å). Both sp^2 centers display slight rehybridization from sp^2 in favor of sp^3. This is best described in terms of a slight contribution of the 1,3 dipolar resonance formula *(1')*. The C8—N1—N2 resonance system is not only twisted about the C8—N1 bond but also about the N1—N2 bond: dihedral angle C1—N2—N1—C3: −18.2° and C1—N2—N1—C8: 158.8°. The other dihedral angles within the five-membered ring amount to: about N1—C3: 19.0°; about C3—C2: −11.5°; about N2—C1: 9.2°; and about C1—C2: 3.0°. Accordingly, the five-membered ring has a slightly twisted envelope conformation with the flap at N1. The normal conformation would be an envelope with the flap at C2. The prime cause of this special feature is the interaction of the $C4F_3$ and $C6H_3$ groups which are positioned *cis* to each other.

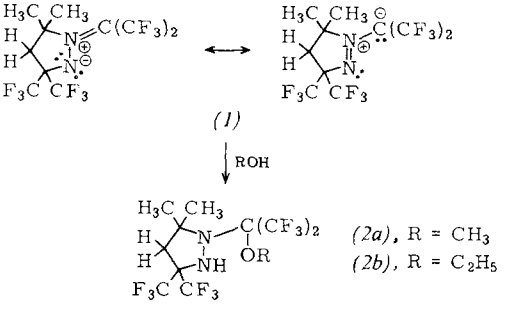
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[1] *T. P. Forshaw* and *A. E. Tipping*, J. Chem. Soc. *C 1971*, 2404.
[2] *W. J. Middleton* and *C. G. Krespan*, J. Org. Chem. *30*, 1398 (1965).
[3] *K. Burger, J. Fehn*, and *W. Thenn*, Angew. Chem. *85*, 541 (1973); Angew. Chem. internat. Edit. *12*, 502 (1973).
[4] *S. E. Armstrong* and *A. E. Tipping*, J. Fluorine Chem. *3*, 119 (1973).
[5] *K. Burger, W. Thenn*, and *A. Gieren*, Angew. Chem. *86*, 481 (1974); Angew. Chem. internat. Edit. *13*, 474 (1974).
[6] *R. Huisgen*, Angew. Chem. *75*, 604 (1963); Angew. Chem. internat. Edit. *2*, 565 (1963).
[7] *W. Hoppe, J. Gassmann*, and *K. Zechmeister* in *F. R. Ahmed*: Crystallographic Computing. Munksgaard, Copenhagen 1970, p. 26.
[8] *A. Gieren*, Chem. Ber. *106*, 288 (1973).

Reactions of Trifluoromethyl-Substituted Azomethinimines with Nucleophiles[1][**]

By *Klaus Burger, Willy Thenn, Helmut Schickaneder*, and *Horst Peuker*[*]

The 1 : 1 intermediate 2-[5,5-dimethyl-3,3-bis(trifluoromethyl)-1*H*$^+$-1-pyrazolinio]-1,1,1,3,3,3-hexafluoro-2-propanide *(1)*, formed by reaction of hexafluoroacetone azine with isobutylene[1, 2] reacts with nucleophiles to form 1 : 1 adducts.



Methanol and ethanol react with *(1)* in a sealed tube at 85 °C to yield 1-(1-methoxy- and 1-(1-ethoxy-2,2,2-trifluoro-1-trifluoromethylethyl)-5,5-dimethyl-3,3-bis(trifluoromethyl)-pyrazolidines *(2a)* and *(2b)* respectively. Their structure follows unequivocally from IR, ^{1}H-NMR, and mass spectra[3]. The reaction *(1)* → *(2)* is reversible on prolonged heating of *(2)* at normal pressure. Methanol adducts have proved of value as a stable storage form and as a convenient neutral source of azomethinimines in the 3,4-dihydroisoquinoline series[4].

On heating for several hours at 80—90 °C or on standing for several weeks at room temperature in a sealed tube, phosphites react with *(1)* to form iminophosphoranes of type

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(4) (Table 1). We consider the intermediacy of species *(3)* having pentacoordinated phosphorus to be quite probable[5]

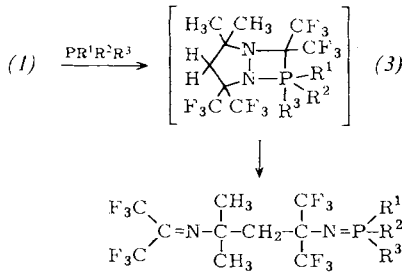


Table 1. Iminophosphoranes of type *(4)*.

(4)	R^1, R^2, R^3	Yield [%]	B.p. [°C/torr] (m.p. [°C])	IR [cm^{-1}] (C=N) [5]
a	$R^1=R^2=R^3=OCH_3$	95	70–71/0.1	1705 [b]
b	$R^1=R^2=R^3=OC_2H_5$	91	92/0.25	1700 [b]
c	$R^1=R^2=R^3=OCH(CH_3)_2$	85	90/0.15	1705 [b]
d	R^1 R^2, $R^3=(OCH_2)_3CC_2H_5$ [a]	71	(100–104)	1705 [c] (very weak)
e	$R^1=OC_2H_5$, $R^2=R^3=C_6H_5$	75	(44)	1705 [c] (very weak)

[a] $PR^1R^2R^3$ = 4-ethyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane.
[b] Film.
[c] In KBr.

The ^{1}H-NMR spectra of *(4)* [δ = 1.48–1.57 (s, $2CH_3$), 2.28–2.39 (d, CH_2)] display a P=N–C–C–H coupling constant of 2.5–3.7 Hz (we found $J_{P-O-C-C-H}$ in 5-alkyl-substituted 2,3-dihydro-1,4,2λ^5-oxazaphospholes to be 1 to 2 Hz[6]); $J_{P-N-C-C-H}$ is reported as 0.6–1.2 Hz[7]. The degradation pattern of the mass spectra[3] M^+, $[M-164]^+$, $[M-206]^+$, $[M-220]^+$ supports the proposed structure *(4)*. The ^{31}P-NMR spectra[8] show the values expected for iminophosphoranes[5].

1-(1-Methoxy-2,2,2-trifluoro-1-trifluoromethylethyl)-5,5-dimethyl-3,3-bis(trifluoromethyl)pyrazolidine (2a)

Compound *(1)*[1] (5.7 g, 15 mmol) and anhydrous methanol (0.64 g, 20 mmol) are heated to 85 °C in a sealed tube for 24 h. After cooling, the crude product is purified by chromatography on a silica gel column (eluant: *n*-hexane), yield 4.05 g (65%) of colorless crystals, m.p. 37–38 °C, ν(NH) = 3250 cm^{-1}. Compound *(2b)* can be obtained in analogous fashion, yield 75%, m.p. 42–43 °C, ν(NH) = 3260 cm^{-1}.

7,7,7-Trifluoro-4,4-dimethyl-2,2,6-tris(trifluoromethyl)-1,5-diaza-5-heptenylidenetrimethoxyphosphorane (4a)

Compound *(1)*[1] (7.68 g, 20 mmol) and trimethylphosphite (2.48 g, 20 mmol) are heated to 80–90 °C in a sealed tube for 12 h. The resulting product is fractionated *in vacuo*, yield 9.8 g.

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[1] Reactions with Hexafluoroacetone Azine, Part 3. – Part 2: *K. Burger, W. Thenn*, and *A. Gieren*, Angew. Chem. *85*, 481 (1974); Angew. Chem. internat. Edit. *13*, 474 (1974).

[2] *A. Gieren, P. Narayanan, K. Burger*, and *W. Thenn*, Angew. Chem. *85*, 482 (1974); Angew. Chem. internat. Edit. *13*, 475 (1974).

[3] *W. Thenn*, Dissertation, Technische Universität München, 1974.

[4] *R. Huisgen, R. Grashey, R. Laur*, and *H. Leitermann*, Angew. Chem. *72*, 416 (1960); *R. Huisgen, ibid. 75*, 604 (1963); Angew. Chem. internat. Edit. *2*, 565 (1963).

[5] *K. Burger, W. Thenn, J. Fehn, A. Gieren*, and *P. Narayanan*, Chem. Ber. *107*, 1526 (1974).

[6] *K. Burger, E. Burgis, J. Albanbauer*, and *L. Schabl*, unpublished results.

[7] *F. Kaplan, G. Singh*, and *H. Zimmer*, J. Phys. Chem. *67*, 2509 (1963).

[8] We are grateful to Doz. Dr. *J. Firl* for recording the ^{31}P-NMR spectra.

[3+2]-Cycloadditions to Trifluoromethyl-Substituted Azomethinimines[1][**]

By *Klaus Burger, Willy Thenn, Reinlinde Rauh*, and *Helmut Schickaneder*[*]

2-[5,5-Dimethyl-3,3-bis(trifluoromethyl)-1*H*$^+$-1-pyrazolinio]-1,1,1,3,3,3-hexafluoro-2-propanide *(1)* is the stable 1:1 adduct of the reaction of hexafluoroacetone azine with isobutylene[2, 3]. The trifluoromethyl-substituted azomethinimine *(1)* is capable of reacting with both electron-rich and electron-poor multiple bond systems according to the scheme of [3+2]-cycloaddition. Mixed "criss-cross" cycloaddition (*i.e.* cycloaddition of two differently substituted double bond systems or of a double

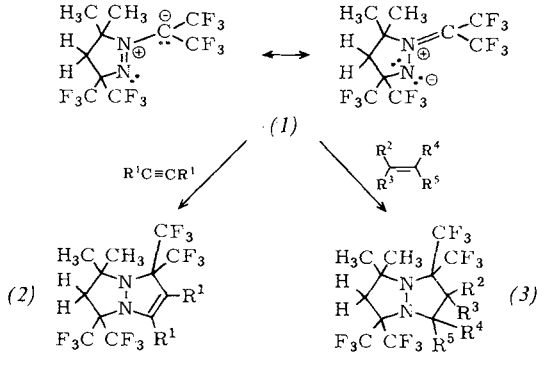


Table 1. 1,5-Diazabicycles of type *(2)* or *(3)* [a].

	Alkyne or alkene	Yield [%]	M.p. [°C]	IR (KBr) [cm^{-1}]
(2a)	tolan	14	120	1640
(2b)	dimethyl acetylene-dicarboxylate	90	77	1760, 1725, 1585
(3a)	cyclopentene	77	38–40	
(3b)	cyclohexene	63	40	
(3c)	maleic anhydride	97	122–123	1895, 1800
(3d)	fumaronitrile	90	120–128	no C≡N absorption

[a] Correct ^{1}H-NMR, ^{19}F-NMR, and mass spectra were obtained for all compounds.

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and a triple bond system in the positions 1,3:2,4 to hexafluoroacetone azine[4, 5]) provides a new general approach to bicyclic heterocycles such as 1,5-diazabicyclo[3.3.0]oct-2-enes *(2)* and 1,5-diazabicyclo[3.3.0]octanes *(3)* (Table 1), as well as their hetero analogs. The intense IR absorption of *(1)* at 1510 cm^{-1} disappears after cycloaddition; it is to be assigned to the azomethinimine system. The first cycloaddition of an azomethinimine to a multiple bond system was reported in 1960 by *Huisgen*[6].

Dimethyl 6,6-dimethyl-4,4,8,8-tetrakis(trifluoromethyl)-1,5-diazabicyclo[3.3.0]oct-2-ene-2,3-dicarboxylate (2b)

Compound *(1)*[2, 3] (3.84 g, 10 mmol) and dimethyl acetylenedicarboxylate (1.42 g, 10 mmol) are heated in anhydrous benzene (40 ml) for 16 h. The crystalline residue obtained on evaporation of the solvent is purified by chromatography (alumina, chloroform) and recrystallized from *n*-hexane, yield 4.72 g.

9,9-Dimethyl-7,7,11,11-tetrakis(trifluoromethyl)-1,8-diazatricyclo[6.3.0.0^{2,6}]undecane (3a)

Compound *(1)* (5.76 g, 15 mmol) and cyclopentene (1.02 g, 15 mmol) are heated to 110 °C in a sealed tube for 3 days. The crude product is purified by column chromatography (alumina, chloroform) and subsequently fractionated *in vacuo*; the colorless fraction of b. p. 50—52 °C/0.05 torr immediately crystallizes, yield 5.25 g.

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[1] Reactions with Hexafluoroacetone Azine, Part 4.—Part 3: *K. Burger, W. Thenn, H. Schickaneder*, and *H. Peuker*, Angew. Chem. 86, 483 (1974); Angew. Chem. internat. Edit. 13, 476 (1974).

[2] *K. Burger, W. Thenn*, and *A. Gieren*, Angew. Chem. 86, 481 (1974); Angew. Chem. internat. Edit. 13, 474 (1974).

[3] *A. Gieren, P. Narayanan, K. Burger*, and *W. Thenn*, Angew. Chem. 86, 482 (1974); Angew. Chem. internat. Edit. 13, 475 (1974).

[4] *W. J. Middleton* and *C. G. Krespan*, J. Org. Chem. 30, 1398 (1965).

[5] *K. Burger, J. Fehn*, and *W. Thenn*, Angew. Chem. 85, 541 (1973); Angew. Chem. internat. Edit. 12, 502 (1973).

[6] *R. Huisgen, R. Fleischmann*, and *A. Eckell*, Tetrahedron Lett. 1960, (12) 1; *R. Huisgen* and *A. Eckell, ibid.* 1960, (12) 5; *R. Huisgen*, Angew. Chem. 75, 604 (1963); Angew. Chem. internat. Edit. 2, 565 (1963).

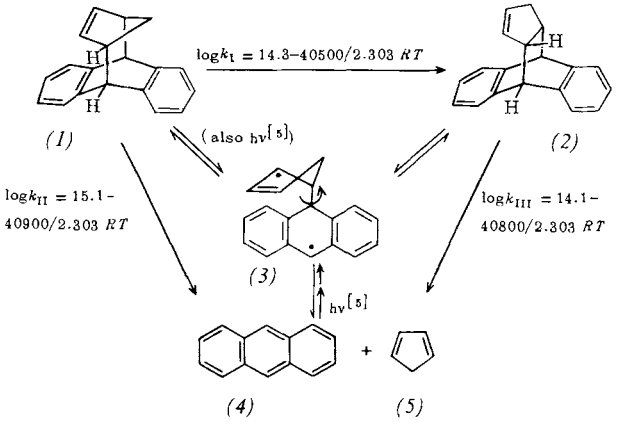
Two-Step Multicenter Reactions: A System in Which "Forbidden" Processes Occur Faster than the "Allowed" Process[**]

By *Gerd Kaupp* and *Rainer Dyllick-Brenzinger*[*]

Application of the Woodward-Hoffmann rules[1] would appear attractive for the planning of syntheses. In such applications predictions of particularly low activation energies for orbital-symmetry allowed concerted reactions and selection rules for thermally or photochemically allowed or forbidden processes are characteristic[1]. The reaction temperatures for two-step (but not for symmetry-forbidden concerted[2]) multicenter reactions can be determined by thermokinetic increment calculations[3]. In order to reach a more reliable decision regarding which reaction conditions are particularly favorable for specific examples within certain reaction classes, it is therefore desirable to experimentally detect, or possibly rule out (short-lived) intermediates[4]. Quantitative measurements on model systems of the type

$$A + B \rightleftharpoons C \rightleftharpoons D \rightleftharpoons A + B$$

are suitable for this purpose. We here report the kinetic detection of a common intermediate in the thermolyses of the cyclopentadiene-anthracene adducts *(1)* and *(2)*[5], reactions which include suprafacial 1,3 shifts and [4+4] and [4+2] cycloreversions (cf. formula scheme), and compare this with the result of photolysis[5].



Both the rearrangement *(1)* → *(2)* (also ^{1}H-NMR detection in hexachlorobutadiene) as well as the formation of anthracene *(4)* from *(1)* and from *(2)* can be followed by UV spectroscopy when oxygen-free *n*-dodecane solutions (0.3 ml; 10^{-4} M) are heated in evacuated ampoules. The following data were determined in order to carry out kinetic analysis:

1) First order rate constants k_{III} at four different temperatures[6] between 214.2 and 246.5 °C from the quantitative formation of *(4)*.

2) Sums of rate constants ($k_I + k_{II}$) at five different temperatures between 186.3 and 226.2 °C from the consumption of *(1)* taking quantitative account of the slight overlapping of the absorption of *(2)* and *(4)* at 282 nm.

3) Increase in concentration of *(4)* from *(1)* at five different temperatures between 173.2 and 214.5 °C up to quantitative cleavage.

4) First order rate constants k_I and k_{II} by evaluation of the integrated rate expression for parallel consecutive reactions[7].

The activation parameters from the Arrhenius plots for k_I, k_{II}, and k_{III} (cf. formula scheme) require an interpretation based on the principle of microscopic reversibility in terms of a common intermediate *(3)*. This appears surprising since the necessarily suprafacial 1,3 shift *(1)* → *(3)* and the [4+4] cleavage *(1)* → *((4)+(5))* is formally forbidden[1], while the [4+2] cleavage *(2)* → *((4)+(5))* is formally allowed[1]. However, such a conclusion follows compellingly from the observations presented below:

1) The Arrhenius activation energies for the processes I, II, and III are equal (within the limits of error).

2) The retro-Diels-Alder reaction of *(2)* ($k_{III} = 1.70 \times 10^{-}$ s^{-1}; 226.2 °C) is not preferred over the reactions of *(1)* ($k_I = 3.72 \times 10^{-4}$, $k_{II} = 1.55 \times 10^{-3}$ s^{-1}; 226.2 °C) but disfavored instead.

3) In contrast to the formation of *(2)* from *(1)* (at 226.2 °C a maximum of 15% after 23 min) the reverse 1,3 shift *(2)* → *(1)* cannot be detected by UV spectroscopy.

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4) Thermochemical increment calculations do not reveal any differences in the molar heats of formation ΔH_f^0 of *(1)* and *(2)* even after taking special account of the H/H interactions (staggered or eclipsed).

Since the adducts *(1)* and *(2)* have (almost) equal energy contents it does not appear surprising that the same activation energies are found for the 1,3 shift and cycloreversions (within the limits of error) if the (possibly polar) diradical *(3)* is formed initially without any change in multiplicity. The "allowed" reaction *(2)*→(*(4)*+*(5)*) is not energetically favored, and the differences in the reaction rates are due almost exclusively to the different frequency factors (cf. formula scheme). The symmetry-corrected rate constant $(k_I+k_{II})/2$ is 5.6 times greater than k_{III} (see above). This kinetic disadvantage of the retro-Diels-Alder reaction suggests that the eclipsed arrangement of benzhydrylic and allylic hydrogen atoms in *(1)* (dihedral angle *ca.* 12°[10]; ^{1}H-NMR coupling constant $J=9.0$ Hz[5]) enhances the probability of cleavage of the C—C bond compared to the staggered arrangement in *(2)* (60°[10]; 3.0 Hz[5]).

In both cases the intermediate *(3)* is formed which has the possibility of rotation about the exocyclic C—C bond, and finally the products (*(4)*+*(5)*) and *(2)* are obtained in the ratio $k_{II}/k_I=80.5/19.5$. In addition, molecular models predict that the stabilization route *(3)*→*(1)* must also be operative. This reaction, which cannot be detected by UV spectroscopy mainly because the primary reaction of *(1)* on pyrolysis is *ca.* 11 times faster, would become of preparative significance if the decomposition of the [4+4] adduct *(1)* could be prevented: selective irradiation of anthracene *(4)* in cyclopentadiene *(5)* (0 C) affords a photointermediate[5] which is likewise assumed to have formula *(3)* (presumably in similar rotational and vibrational states). Kinetically controlled reaction then yields *(1)* and *(2)* in the ratio 58/42[5].

The utility of direct comparison of thermal and photochemical two-step reactions is apparent from the results obtained on irradiation of adduct *(1)*[11]. The "allowed" reactions afford 80% of *(4)* and 18% of *(2)* ($\phi=0.26+0.06$; CH_3CN; 20 C)[5]. The measurable deactivation ratio of thermally and photochemically generated *(3)* is thus, as expected, equal (within the limits of error). Hence the conclusion is justified that intermediate *(3)* generated from *(1)* undergoes stabilization to (*(4)*+*(5)*), *(1)*, and *(2)* in the ratios 4.1:1.4:1.0.

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[1] *R. B. Woodward* and *R. Hoffmann*: The Conservation of Orbital Symmetry. 2nd Edit. Verlag Chemie, Weinheim 1972.

[2] *J. A. Berson* and *R. W. Holder*, J. Amer. Chem. Soc. 95, 2037 (1973); and literature cited therein.

[3] *S. W. Benson*: Thermochemical Kinetics. Wiley, New York 1968; *R. K. Lyon*, J. Org. Chem. 34, 3202 (1969).

[4] Apparently owing to difficulties of measurement a decision of this kind has not yet been reached for thermolyses of 1,5-cyclooctadiene and 4-vinylcyclohexene to butadiene, cf. *W. v. E. Doering, M. Franck-Neumann, D. Hasselmann*, and *R. L. Kaye*, J. Amer. Chem. Soc. 94, 3833 (1972).

[5] *G. Kaupp*, Angew. Chem. 84, 718 (1972); Angew. Chem. internat. Edit. 11, 718 (1972); Liebigs Ann. Chem. 1973, 844.

[6] Temperature constancy ±0.1 °C; measurements conducted in an ultrathermostat (Lauda, type R 10/2) with calibrated fine thermometers.

[7] Adjustment of k_{II} (from less precisely determinable initial rates; variation in steps of 0.3%) by using the more accurately determinable quantities

$$k_I=\left[\frac{[(4)]-[(1)]_0}{[(1)]_0}+\frac{k_{II}}{(k_I+k_{II})}\exp\langle-(k_I+k_{II})t\rangle\right]\frac{(k_I+k_{II})(k_{III}-k_I-k_{II})}{(k_I+k_{II})\exp\langle-k_{III}t\rangle-k_{III}\exp\langle-(k_I+k_{II})t\rangle} \quad (1)$$

in order to meet eq. (1) (standard deviation of k_I: <3%) [8]; eq. (1) can be derived from the system of integrated rate equations for parallel consecutive reactions with crosslinked chains [9] since *(3)* does not display significant enrichment.

[8] *R. Dyllick-Brenzinger*, Diplomarbeit, Universität Freiburg 1973.

[9] *N. M. Rodiguin* and *E. N. Rodiguina*: Consecutive Chemical Reactions. Van Nostrand, Princeton 1964, pp. 55ff.

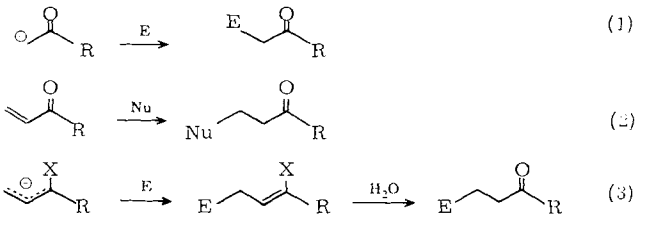
[10] Measured on Framework Molecular Models. Prentice-Hall, Englewood (USA).

[11] As in the thermolysis, the photolysis of *(2)* [5] should also be disfavored for conformative reasons.

Doubly Metalated 2-Propene-1-thiol Thioacrolein Dianion[1][**]

By *Karlheinz Geiss, Bernhard Seuring, Reimund Pieter*, and *Dieter Seebach*[*]

As exemplified by eq. (1) and (2), carbonyl compounds add electrophiles (E) at the α position (E^2 reaction[2]) and nucleophiles (Nu) at the β position (N^3 reaction[2]). *Umpolung* at C^3 is, in principle, possible with heterosubstituted allylic anions provided that they are susceptible to attack by electrophiles at the γ position to the hetero atom; with X=SR the α position is preferentially attacked [eq. (3)][2, 3]

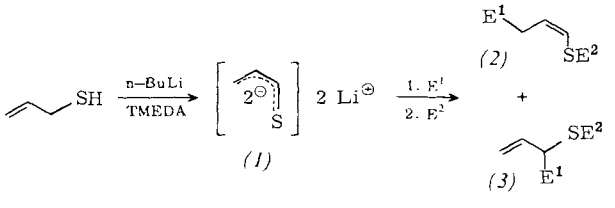


(1)

(2)

(3)

In this communication we report a novel allylic anion, the doubly metalated 2-propenethiol *(1)*[4, 5], which reacts preferentially in the γ position with a variety of electrophiles, including alkyl and benzyl chlorides and bromides, epoxides, aliphatic, cycloaliphatic, aromatic aldehydes and ketones, and dimethyl disulfide. The dilithio derivative is formed quantitatively by treating a 0.3—0.9 M solution of the thiol in THF with 2.1 equivalents of *n*-butyllithium (1.6 M in *n*-hexane) in the presence of 1—2 equivalents of tetramethylethylenediamine (TMEDA) for four hours at 0 °C. As shown in Table 1, the γ/α ratios[6] in which products *(2)* and *(3)* are formed range from 67:33 to 80:20 (NMR spectrum). The γ adducts



(1)

(2)

(3)

are formed almost exclusively (>95%) in the *cis*-configuration[6]. The isomers *(2)* and *(3)* may be separated by preparative thin-layer, column, or gas chromatography.

The use of *(1)* as synthon in analogy to eq. (3) is demonstrated by the reaction of the products *(4)* and *(8)* of type *(2)* in Scheme 1. We have developed a new procedure for the

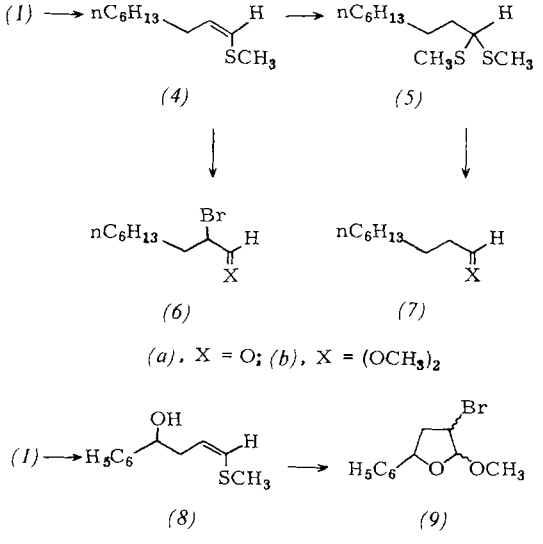
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Table 1. Yield, reaction conditions, and γ/α ratios in the reactions of *(1)* with electrophiles to give *(2)* + *(3)*.

E^1	E^2	Reaction conditions [a]	Yields [%] of *(2)* + *(3)* [b]	γ/α Ratio [= *(2)*/*(3)*]
C_2H_5Br	C_2H_5Br	A	65	77/23
n-$C_{10}H_{21}Br$	n-$C_{10}H_{21}Br$	A	90	77/23
$C_6H_5CH_2Br$	$C_6H_5CH_2Br$	A	67	73/27
n-$C_5H_{11}Cl$	CH_3I	C	75	76/24
n-$C_6H_{13}Br$	CH_3I	C	90	78/22 [c]
n-C_8H_{17}-Cl	CH_3I	C	87	74/26
i-C_3H_7-Cl	$C_6H_5CH_2Br$	C	80	68/32
$(CH_3)_3SiCl$	$C_6H_5CH_2Br$	B	76	76/24
2,2-Dimethyloxirane	2,2-Dimethyloxirane	A	86	78/22
C_2H_5CHO	CH_3I	B	69	74/26
C_6H_5CHO	CH_3I	C	89	67/33
Cyclopentanone	CH_3I	C	70	69/31
$C_6H_5COCH_3$	CH_3I	C	95	70/30
$(C_6H_5)_2CO$	CH_3I	C	88	75/25
CH_3SSCH_3	CH_3I	B	70	80/20

[a] A: 2.1 equivalents of E^1 are added at −80 C by syringe, then the mixture is allowed to warm to 20 C overnight. B: *(1)* is reacted with 1.03 – 1.1 equivalents of E^1 for 1 h at −80 C, 1.1 equivalent of E^2 is added, and the mixture warmed to room temperature. C: as B, but E^2 is added *after* slowly warming to room temperature. Workup see ref. [4].
[b] The yields (not optimized) were determined by NMR spectroscopy of the crude products of 2–10 mmol runs.
[c] See Scheme 1, compound *(4)*.



Scheme 1. Sulfur-free products from adducts *(4)* and *(8)* of the dianion *(1)* (all reactions were carried out at 20 C). *(4)*→*(5)*: CH_3SH/HCl gas in benzene, 3 min, 100%; *(4)*→*(6a)*: 4,5 equiv. NBS in acetonitrile/H_2O, 2 min, 73%; *(4)*→*(6b)*: as above but in anhydrous CH_3OH, 85%; *(5)*→*(7a)*: 4.5 equiv. NBS, 5 equiv. $AgNO_3$ in acetonitrile/H_2O, 3 min, 60%; *(5)*→*(7b)*: as above but in anhydrous CH_3OH, 70%; *(8)*→*(9)*: 4.3 equiv. NBS in CH_3OH, 2 min, 74%.

conversion of methyl vinyl thioethers such as *(4)* into aldehydes *(7a)* which involves addition of thiol to form a thioacetal *(5)* that is subsequently hydrolyzed by known methods[2]. *N*-Bromosuccinimide[7] converts *(4)* into the α-bromo aldehyde *(6a)* in aqueous acetonitrile, while the bromo acetal *(6b)* is produced in methanol; similarly, the cyclic bromo acetal *(9)* is formed from the benzaldehyde adduct *(8)*.

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[1] From the PhD thesis of *K.-H. Geiss* and the Diplomarbeit of *B. Seuring*, Universität Giessen 1974.

[2] Reviews on *Umpolung* of carbonyl reactivity: *D. Seebach* and *M. Kolb*, Chem. Ind. (London), *1974*, in press; *D. Seebach*, Angew. Chem. *81*, 690 (1969); Angew. Chem. internat. Edit. *8*, 639 (1969); *D. Seebach*, Synthesis *1969*, 17, and literature cited therein.

[3] *E. J. Corey* and *B. W. Erickson*, unpublished results 1966/67; *B. W. Erickson*, PhD thesis, Harvard University 1970; *J. F. Biellmann* and *J. B. Duceb*, Tetrahedron Letters *1968*, 5629; *1969*, 3707; *K. Kondo et al.*, Chem. Commun. *1972*, 1311; *D. Seebach*, *M. Kolb*, and *B.-Th. Gröbel*, Angew. Chem. *85*, 42 (1973); Angew. Chem. internat. Edit. *12*, 69 (1973); *P. L. Stotter* and *R. E. Hornish*, J. Amer. Chem. Soc. *95*, 4444 (1973); *K. Oshima et al.*, *ibid. 95*, 2693, 4446, 5803, 7926 (1973); *D. A. Evans* and *G. C. Andrews*, Accounts Chem. Res. 7, 1974, in press, and literature cited therein.

[4] Doubly metalated thiobenzyl alcohol: *D. Seebach* and *K.-H. Geiss*, Angew. Chem. *86*, 202 (1974); Angew. Chem. internat. Edit. *13*, 202 (1974).

[5] Prof. *M. Schlosser*, Lausanne, kindly informed us that 2-propene-1-thiol and 3-methyl-2-butene-1-thiol have been doubly metalated independently in his laboratories.

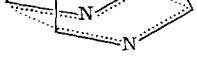
[6] Determined from the NMR integration ratios of the following signals: α-sulfur hydrogens of the group E^2, the vinylic *versus* all other hydrogens, and the terminal vinylic hydrogens *versus* all vinylic hydrogens. The NMR spectra of some of our products are identical with those described by *B. W. Erickson* (Thesis, Harvard University 1970) who obtained compounds *(2)* and *(3)* from metalated thioallyl ethers. All new products show spectra in accordance with the structures given here.

[7] *E. J. Corey* and *B. W. Erickson*, J. Org. Chem. *36*, 3553 (1971).

Dynamic Stereochemistry of the Degenerate Diaza-Cope Rearrangement[**]

By *Fritz Vögtle* and *Ernst Goldschmitt*[*]

A further milestone was passed in the theory of valence isomerization when, in 1971, *Dewar*[1] postulated that 3,7-diazasemibullvalene has to be formulated as a nonclassical molecule [bishomopyrazine *(1)*] in the ground state.

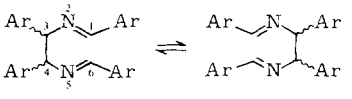


(1)

While experimental proof of this prediction is still forthcoming, the recently described thermal valence isomerization of 1,3,4,6-

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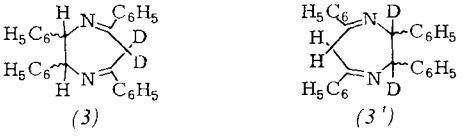
(2) (2')

(a), Ar = phenyl
(b), Ar = 4-methylphenyl
(c), Ar = 4-methoxyphenyl
(d), Ar = 4-cyanophenyl
(e), Ar = 4-pyridyl
(f), Ar = 2-pyridyl

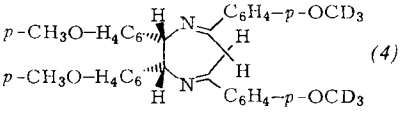
tetraaryl-2,5-diazahexadienes[2], whose *degenerate* variant *(2)*⇌*(2')* is reported in the present communication, permits analogous studies of heteroatom and substituent effects in a nonbridged model system.

At elevated temperatures (above 120 °C in D_6-DMSO) the diaza-Cope rearrangement *(2a)*⇌*(2a')* of *N,N'*-dibenzylidene-1,2-diphenylethylenediamine leads to an equilibrium between *meso*- and *d,l*-valence isomers in the ratio 1 : 1, irrespective of whether the reaction starts from *meso-(2a)* (m. p. 171—173 C; 164—165 C[3]) or *d,l-(2a)* (m. p. 159—160 C). This was established by proton magnetic resonance comparisons with authentic *meso*- and *d,l* compounds (Fig. 1).

Thus the deuterium-labeled azomethine *meso-(3)* obtained on reaction of *meso*-1,2-diphenylethylenediamine with [formyl-D]-benzaldehyde affords a completely equilibrated 1 : 1 : 1 : 1 valence isomer mixture of *meso*- and *d,l-(3)* and *-(3')* whose components can be distinguished by their proton resonance. An analogous equilibration is observed starting from *meso-(4)*.



(3) (3')



(4)

Comparison of the ^{1}H-NMR signal intensities at 139, 146, and 152 C as functions of time affords an approximate value of 31 kcal/mol for the free enthalpy of activation $\Delta G^{\neq}$ of the *d,l*→*meso* transition of *(2a)* which is to be regarded as constitutionally but not configuratively degenerate.

It is particularly appealing that the degenerate diaza-Cope rearrangements can be observed directly by dynamic ^{1}H-NMR spectroscopy (Fig. 1): on heating of a sample of *d,l-(2a)* dissolved in D_6-DMSO the initial reaction is the above *d,l*⇌*meso* isomerization, which is readily recognized by appearance of CH=N—CH proton resonances of the *meso* compound. A further increase in temperature leads to increasing broadening of the H^1,H^3- and H^4,H^6 signals of the *d,l* form; they again appear as sharp singlets on cooling of the sample solution. Accordingly, *d,l-(2a)* is a *molecule having a fluctional structure* at elevated temperatures.

The free energy of activation at the extrapolated coalescence temperature ($T_c \approx 220$—230 °C; $\Delta\nu = 209$ Hz) has a value of 23—24 kcal/mol and is thus lower than in open-chain Cope systems (1,5-hexadienes)[1,4]. Remarkably, the signals of *meso-(2a)* remain as sharp singlets in this temperature range (Fig. 1). This finding is in accord with calculations[1,4] and experimental results[5] which indicate that the boat-like six-center transition state—which would have to be traversed in the case of a valence isomerization *meso-(2a)*⇌*meso-(2a')*[2]—requires a higher activation energy than the chair-like four-center transition state which is to be assumed for the *d,l*⇌*d,l* conversion[6]. A further argument for the greater tendency of the *d,l* form to rearrange compared to the *meso* form could lie

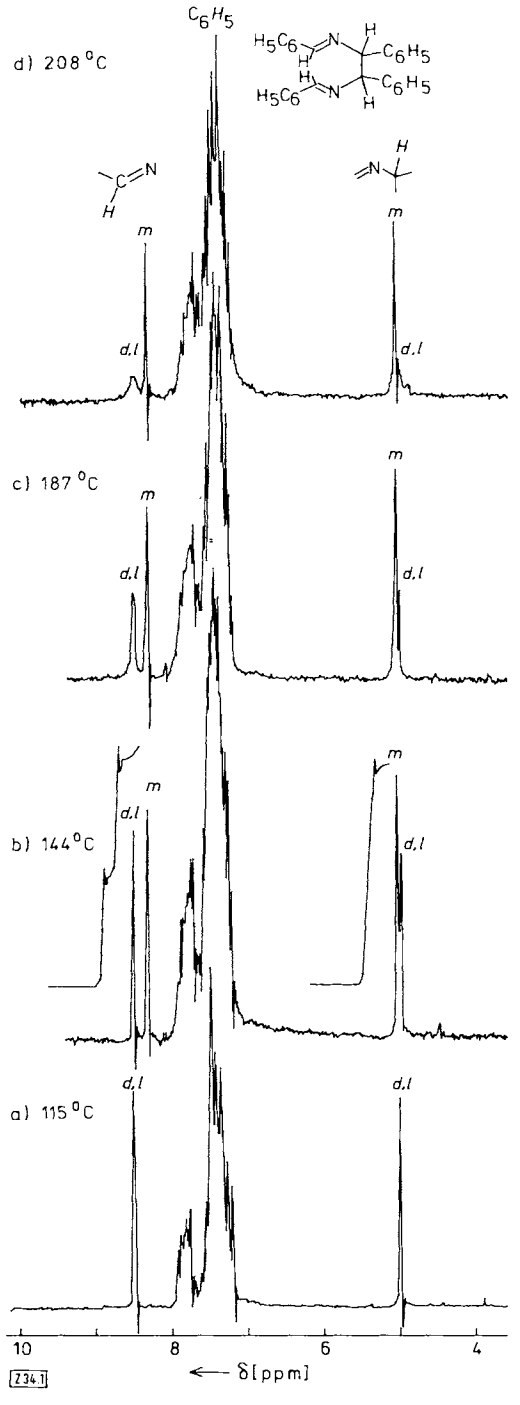
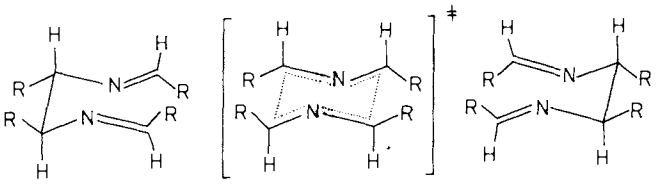


Fig. 1. Temperature-dependent proton resonance (sections) of *d,l-(2a)* (60 MHz in D_6DMSO). *d,l*: signals of the *d,l* compound; *m*: signals of the *meso* form.

in the *d,l* compound being conformationally more favorable for the chair transition state whereas the conformation of the *meso* compound is unfavorable for the boat transition state. This becomes clear on consideration of molecular models.

For kinetic determination of the activation parameters of the *d,l*⇌*d,l* valence isomerization, we resolved racemic 1,2-diphenylethylenediamine into the antipodes with the aid of optically active tartaric acid[7]. (+)-*(2a)* and (−)-*(2a)* were obtained in crystalline form. Their racemization, which is due to a [3.3]-sigmatropic shift, was pursued by polarimetry at several different temperatures. The rate of valence isomerization is already too high for polarimetric measurements at 70 °C. Racemization of the optical antipodes in the course of the diaza-Cope rearrangement is readily understood in

view of the mirror image geometry of the substituents in the transition state (Fig. 2). The rearrangement obeys first order kinetics at all temperatures ($k_{31.8\,°C}=5.23\times10^{-5}$, $k_{41.4\,°C}=1.50\times10^{-4}$, $k_{45.0\,°C}=2.39\times10^{-4}$, $k_{48.6\,°C}=3.53\times10^{-4}$). The activation energy E_A for the degenerate diaza-Cope rearrangement is found to be 21.8 kcal/mol. Interestingly, a value of 23.9 kcal/mol is obtained for $\Delta G^{\neq}$, which agrees with that determined by the coalescence method. As expected, the entropy of activation is strongly negative: $\Delta S^{\neq}=-7.5$ cal deg^{-1} mol^{-1}.



[Z 34 2]

Fig. 2. Racemization (*S,S*)-(*2*)→(*R,R*)-(*2'*) or (*R,R*)-(*2*)→(*S,S*)-(*2'*). The mirror image in the transition state is shown gray.

The degenerate diaza-Cope rearrangement even appears to take place in the solid state: crystals of (−)-(*2a*) lose their optical rotatory power within 24 h.

Introduction of *o*, *m*, or *p* substituents into the four aromatic nuclei of (*2*) leads to further degenerate diaza-Cope systems. The compounds studied hitherto confirm the results obtained with the unsubstituted system (*2a*): only minimal changes are found in the activation parameters of (*2b*) and (*2c*). In the presence of electron-attracting substituents as in (*2d*)—(*2f*) avoidance reactions occur which are possibly attributable to an irreversible cleavage of the weakened allyl σ bond. The considerable influence of the 3,4 phenyl substituents of (*2a*) is underlined by the lack of any tendency of *N,N'*-dibenzylideneethylenediamine to undergo rearrangement at 210 °C.

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[1] *M. J. S. Dewar* and *D. H. Lo*, J. Amer. Chem. Soc. *93*, 7201 (1971); *M. J. S. Dewar, Z. Nahlovska*, and *D. Nahlovska*, Chem. Commun. *1971*, 1373; cf. also *R. Hoffmann* and *W. D. Stohrer*, J. Amer. Chem. Soc. *93*, 6941 (1971).

[2] *F. Vögtle* and *E. Goldschmitt*, Angew. Chem. *85*, 824 (1973); Angew. Chem. internat. Edit. *12*, 767 (1973); Nachr. Chem. Techn. *21*, 282 (1973); Chem. Ind. (London) *1973*, 1072.

[3] *G. Grossmann*, Ber. Deut. Chem. Ges. *22*, 2298 (1889).

[4] *H. M. Frey* and *R. Walsh*, Chem. Rev. *69*, 103 (1969).

[5] *W. v. E. Doering* and *W. R. Roth*, Tetrahedron *18*, 67 (1962).

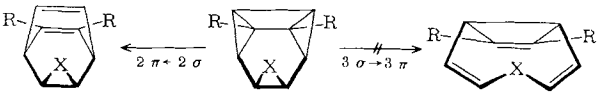
[6] In contrast, a *meso*→*meso* valence isomerization is possible under mild conditions in the salicyl-substituted system which is characterized by H-bonding effects and keto-enol tautomerism [2].

[7] *I. Lifschitz* and *J. G. Bos*, Rec. Trav. Chim. Pays-Bas *59*, 173 (1940).

Simple Bridged *cis*-Oxa- and *cis*-Aza-tris-σ-homobenzene Systems; Synthesis and 3σ→3π Isomerization[**]

By *Horst Prinzbach, Shinzo Kagabu*, and *Hans Fritz*[*]

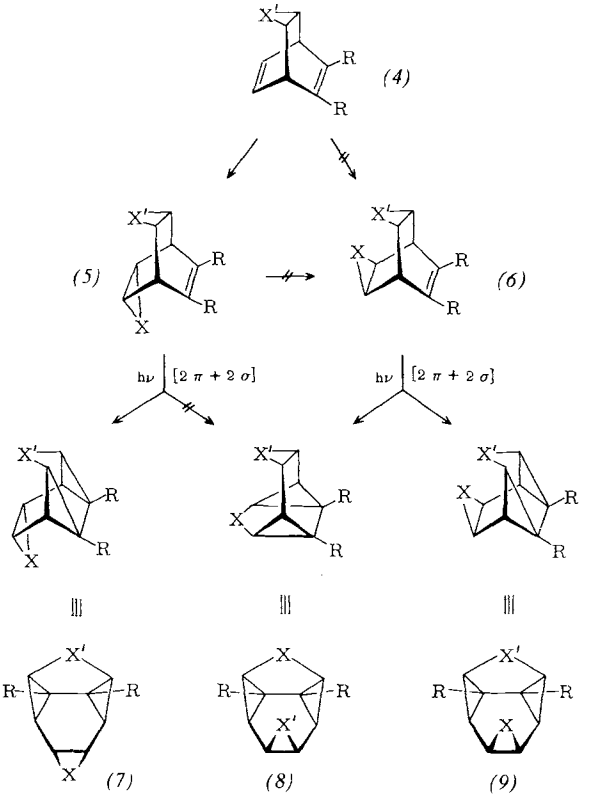
The zero-bridged *cis*-tris-σ-homobenzene compounds (*2*) (X = CH_2, $CHCO_2CH_3$, O; R = CO_2CH_3, CF_3, CH_3) occupy a special position in that their thermolysis proceeds not *via* the usual 3σ→3π cleavage to (*3*) (6-electron process) but *via* 2σ→2π cleavage to (*1*) (4-electron process)[1]. The hypothesis that the multiply annelated four-membered ring is responsible for this behavior was to be tested on a model of *cis*-tris-σ-homobenzene systems having a longer bridge, *e.g.* (*8*) or (*9*). [2π+2σ]-photocyclization of the bishomobarrelenes (*5*) or (*6*) appeared a likely method for their preparation.



(*1*) (*2*) (*3*)

These expectations were not fulfilled however; photoreactions with various *endo,exo*-bishomobarrelenes (*5*) (X,X' = CH_2, $CHCO_2CH_3$, O, NR'; R = CO_2CH_3, CF_3, CH_3) afford almost exclusively the *trans*-tris-σ-homobenzene products (*7*), which are incapable of 3σ→3π opening, with participation of the three-membered ring *anti* to the excited chromophore. The *endo,endo*-bishomobarrelenes (*6*)—both possibilities of [2π+2σ]-addition lead to *cis* products [(*8*), (*9*)]—are, however, inaccessible. Regardless of the nature of the three-membered ring in (*4*) (X' = CH_2, CHCN, O), the second three-membered ring is only formed from the *exo* side (X = CH_2, $CHCO_2CH_3$, O, NR') to give (*5*) under a wide variety of conditions[2, 3]. The steric conditions and the proclivity to rearrangement of the tricyclo[3.2.2]nonane skeleton also thwarted attempts to bring about a transition (*5*)→(*6*) by way of known substitution and cyclization steps[3].

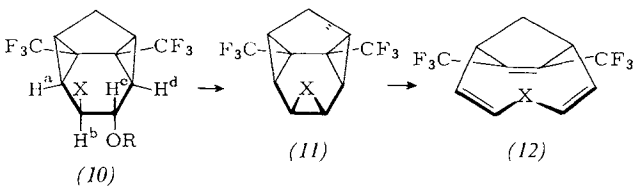
This *exo-endo* isomerization is however possible at the stage of (*7*). The "*trans*-oxide" (*7*) (X = O, X' = CH_2, R = CF_3)[3], which is accessible from (*5*) (X = O, X' = CH_2, R = CF_3) on a preparative scale by direct photoexcitation and is highly resistant to attack by nucleophiles, undergoes smooth reaction in a 2 N sulfuric acid solution in DMSO to give the crystalline *trans*-diol (*10a*) (72%; m.p. 112 °C; τ = 5.87 (H^b), 6.26 (H^c); $J_{b,a}=4.2$, $J_{b,c}\approx6$, $J_{c,d}\approx0$ Hz; CD_3COCD_3, 270 MHz). The action of *ca.* 1 equiv. of tosyl chloride (pyridine, 20 °C, 3 d) results in 60% conversion to a mixture of unchanged (*10a*) and the bistosylate (*10c*) (colorless needles, m.p. 127—128 °C;



(*4*) (*5*) (*6*) (*7*) (*8*) (*9*)

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(10) *(11)* *(12)*

(a), X = OH, R = H
(b), X = OH, R = tosyl
(c), X = *O*-Tosyl, R = tosyl
(d), X = N_3, R = H
(e), X = N_3, R = tosyl

(a), X = O
(b), X = NH
(c), X = $NCOCH_3$

ca. 30%; $\tau = 4.91$ (H^b), 5.23 (H^c); $J_{b,a} \approx 6.5$, $J_{b,c} = 3.7$, $J_{c,d} \approx 1$ Hz; $CDCl_3$; 270 MHz) which is also found to contain a monotosylate (colorless needles, m. p. 106—107 °C; *ca.* 20%) on chromatography (silica gel, CH_2Cl_2), shown by the ^{1}H-NMR data ($\tau = 5.55$ (H^b), 5.45 (H^c); $J_{b,a} = 4.5$, $J_{b,c} = 5.3$, $J_{c,d} \approx 0$ Hz; $CDCl_3$, 270 MHz) to be the desired *exo*-ester *(10b)*.

In accord with the conformational mobility in the skeleton *(10)*, evidenced *inter alia* by the substituent-dependent coupling constants, cyclization of *(10b)* to the *cis*-monooxa-tris-σ-homobenzene *(11a)* (colorless crystals, m. p. 50—51 C; 82%) can be performed under conventional conditions (sodium methoxide, ether, 20 C). For preparation of the "*cis*-imine" *(11b)* we resorted to the reaction sequence which has proved its value in the synthesis of *cis*-"benzene triimine" from *cis*-"benzene trioxide"[4]. In the presence of a little concentrated sulfuric acid, *(7)* (X = O, X' = CH_2, R = CF_3) reacts selectively with an excess of sodium azide in DMSO (130 C) to form the *trans*-azido alcohol *(10d)* (colorless crystals, 68%, m.p. 82.5—83 C; $\tau = 5.98$ (H^b), 6.20 (H^c); $J_{a,b} = 4.2$, $J_{b,c} = 7.0$ $J_{c,d} \approx 0$ Hz; $CDCl_3$, 270 MHz). After esterification to give *(10e)* (tosyl chloride, pyridine; colorless needles, 96%, m.p. 105.5—106.5 C), reduction and cyclization to *(11b)* can be accomplished with $NaAlH_4$ in THF (colorless crystals, m. p. 87.5—88.5 °C, 55%). Acetylation in pyridine/acetic anhydride to give *(11c)* (m.p. 75—76 °C) is almost quantitative.

The bis(trifluoromethyl)tris-σ-homobenzene compounds *(11a)*—*(11c)* are more stable thermally than the unbridged oxa- or aza-analogous diesters[1]. Above 160 C and 140 C *(11a)* and *(11c)* respectively—unlike the homologs *(2)*—undergo fast, uniform, irreversible 3σ→3π cleavage to form the bridged heterononatrienes *(12a)* (colorless crystals, m.p. 17—18 C) and *(12c)* (yellowish crystals, m.p. 75—76 C). The structures *(10)*—*(12)* are confirmed by physical data (UV, IR, MS, ^{1}H- and ^{13}C-NMR) and elemental analyses. The characteristic coupling constants used for spectroscopic identification of the *cis-trans* isomers *(11)* and *(7)*, and also the trienes *(12)*, are in good agreement with the values for the unbridged oxa- and aza-σ/π-trishomobenzenes[5].

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[1] *H. Prinzbach, W. Eberbach*, and *G. Philippossian*, Angew. Chem. *80*, 910 (1968); Angew. Chem. internat. Edit. *7*, 887 (1968); *R. S. Liu*, Tetrahedron Lett. *1969*, 1409; *H. Prinzbach, H. Fritz, H. Hagemann, D. Hunkler, S. Kagabu*, and *G. Philippossian*, Chem. Ber. *107*, 1971 (1974).

[2] *H. Prinzbach, M. Klaus*, and *W. Mayer*, Angew. Chem. *81*, 902 (1969); Angew. Chem. internat. Edit. *8*, 883 (1969); *H. Prinzbach* and *S. Kagabu*, unpublished; cf. *A. de Meijere* and *C. Weitemeyer*, Angew. Chem. *82*, 359 (1970); Angew. Chem. internat. Edit. *9*, 376 (1970).

[3] *H. Prinzbach, D. Forster, D. Hunkler*, and *S. Kagabu*, to be published.

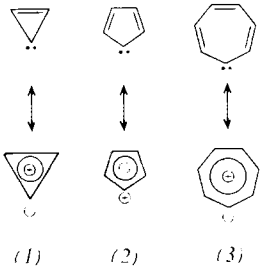
[4] *R. Schwesinger* and *H. Prinzbach*, Angew. Chem. *85*, 1107 (1973); Angew. Chem. internat. Edit. *12*, 989 (1973).

[5] *H. Prinzbach* and *D. Stusche*, Angew. Chem. *82*, 536 (1970); Angew. Chem. internat. Edit. *9*, 799 (1970); *H. Prinzbach* and *D. Stusche*, Helv. Chim. Acta *54*, 755 (1971).

Proof of the Electrophilic Character of Cyclopentadienylidene[**]

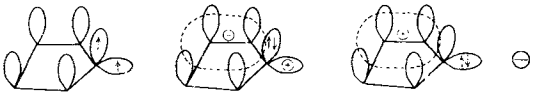
By *Heinz Dürr* and *Franz Werndorff*[*]

According to EHT calculations[1] the electrophilic or nucleophilic character ought to alternate[2] in the series of cyclic carbenes *(1)*—*(3)*. Compound *(3)* has recently been shown to exhibit the expected nucleophilic character[3].



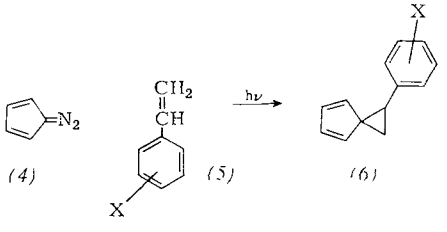
(1) *(2)* *(3)*

In the case of the carbene cyclopentadienylidene *(2)* essentially three configurations are possible: the triplet σ_p and the singlets p^2 (aromatic) and σ^2 (antiaromatic). σ^2-*(2)* should participate in nucleophilic additions whereas p^2-*(2)* should participate in electrophilic additions[2]. The ground state of *(2)* at 77 °K is the triplet p-*(2)*[2] (ESR).



$\sigma p(T_1)$ $p^2(S_0)$ $\sigma^2(S_2)$

A criterion for electrophilic or nucleophilic character of a carbene is its rate of addition to variously alkylated olefin pairs. In the case of *(2)*, *Moss*[4] was unable to clarify this



(4) *(5)* *(6)*

Table 1. Phenylspiroheptadienes *(6a)*—*(6e)* obtained by [1+2]cycloaddition of cyclopentadienylidenes *(2)* to the styrenes *(5a)*—*(5e)* [a].

	X	*(6)*, yield [%] [b]	k_{rel} [c]
a	H	18	—
b	*p*-CH_3	12	$1.2_1 \pm 0.1$
c	*p*-CH_3O	17	$1.9_5 \pm 0.3$
d	*p*-Cl	12	$0.6_0 \pm 0.1$
e	*m*-Br	7	$0.5_5 \pm 0.04$

[a] The structure of *(6)* was confirmed spectroscopically; formation of a pyrazoline from *(5)* and *(4)* was ruled out by control experiments.

[b] Obtained by photolysis of *(4)* in the styrenes *(5)* (high-pressure Hg-vapor lamp. GW_v filter: $\lambda > 360$ nm, 20 ± 1 °C. 60—91% of calculated N_2).

[c] For determination of k_{rel} the photolysis of *(4)* was carried out in equimolar mixtures of *(5a)* and one of the other styrenes *(5)* (75% N_2). The spiroheptadiene mixture of *(6a)* and *(6x)* was filtered over silica gel and then analyzed gas chromatographically (2—3 m columns, 20% SE 30 on Chromosorb PAW 30—60 mesh, 160—170 °C); the results (5 measurements) were evaluated using eq. (2).

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[**] Cycloalkenecarbenes Part 11.—Part 10: *H. Dürr, B. Ruge*, and *B. Weiss*, Liebigs Ann. Chem., in press.

problem—which can be regarded as a decisive test for *Hoffmann*'s calculation[1]. We now describe the [1+2]-cycloaddition of *(2)* to styrenes *(5)* containing *p* or *m*-substituents of different electronegativity. Unlike in Ref. [4] steric effects are excluded. The singlet character of *(2)* at room temperature, a prerequisite for such studies as these, was proven by its stereospecific cycloaddition to *cis*- or *trans*-olefins[4]. The competition constants k_{rel} (Table 1) for the cycloaddition of *(2)* [from diazocyclopentadiene *(4)*] to styrene pairs should therefore permit conclusions to be drawn regarding the nucleophilic or electrophilic character as well as the electronic configuration of *(2)*. For the determination of k_{rel}, eq. (1) can, under the reaction conditions—twentyfold excess of styrene and equimolar mixture *(5a)*/*(5x)*—be simplified to eq. (2) [*(5x)*=*(5b)* to *(5e)*].

Correlation of k_{rel} with Hammet σ constants[5] yields a reaction constant of $\rho = -0.76 \pm 0.10$ (correlation with the σ^+ values[5]: $\rho = -0.46 \pm 0.05$).

$$k_{rel} = \frac{k_B}{k_A} = \frac{\log([B_0]/[B])}{\log([A_0]/[A])} \quad (1)$$

$$k_{rel} = [(6b)-(6e)]/[(6a)] = k_{(6x)} \cdot k_{(6a)}. \quad (2)$$

k_A and k_B = rates of addition to *(5a)* and *(5x)* resp.

These values confirm quite clearly the electrophilic character of *(2)* and therewith the alternance between electrophilicity and nucleophilicity in the carbene series *(2)* and *(3)*; moreover, the p^2 electronic configuration of the reactive species at room temperature can be regarded as confirmed.

Received: March 19, 1974 [Z 18 IE]
German version: Angew. Chem. *86*, 413 (1974)

[1] *R. Gleiter* and *R. Hoffmann*, J. Amer. Chem. Soc. *90*, 5457 (1968).

[2] *H. Dürr*, Fortschr. Chem. Forsch. *40*, 103 (1973).

[3] *L. W. Christensen, E. E. Waali*, and *W. M. Jones*, J. Amer. Chem. Soc. *94*, 2118 (1972).

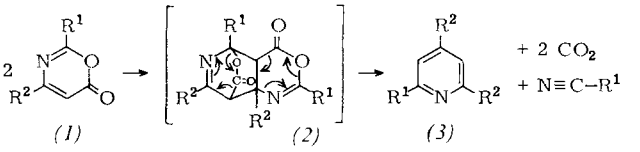
[4] *R. A. Moss*, J. Org. Chem. *31*, 3296 (1966); *R. A. Moss* and *J. R. Przybyla*, *ibid. 33*, 3816 (1968).

[5] *L. P. Hammett*: Physikalische Organische Chemie. Verlag Chemie, Weinheim 1973.

Thermolysis of 1,3-Oxazin-6-ones to 2,4,6-Trisubstituted Pyridines[1]

By *Ernst Buschmann* and *Wolfgang Steglich*[*]

On heating to 270 °C β-acylaminoacrylates afford 1,3-oxazin-6-ones *(1)*[1], which on prolonged heating on a hot-metal bath (300—320 °C) undergo further reaction to give 2,4,6-trisubstituted pyridines *(3)*, nitriles, and CO_2.

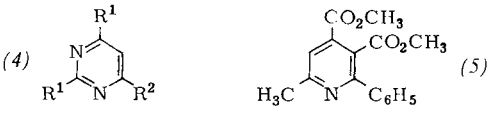


(1) *(2)* *(3)*

In the case of *(1a)*—*(1c)* 2,4,6-trisubstituted pyrimidines *(4)* are formed as by-products. They remain in the distillation flask after *(3)* has been distilled off and can be isolated in an analytically pure state by preparative gas chromatography (Table 1).

The trialkyl-substituted pyridines and pyrimidines can be readily distinguished from each other by characteristic IR bands (CCl_4) at 1605, 1570 [*(3a)*—*(3d)*][2] and 1595, 1560 cm^{-1} [*(4a)*—*(4c)*] respectively. The NMR spectra are in accord with the given structures.

The formation of pyridines, nitriles, and CO_2 can be explained in terms of the Diels-Alder dimer *(2)*. As in the reaction



(4) *(5)*

Table 1. Pyridines *(3)* and pyrimidines *(4)* prepared [a].

Oxazinone *(1)*	R^1	R^2	Thermolysis conditions	Product	Yield [%]	B.p. [°C/torr]
(1a) [b]	CH_3	CH_3	3 h, 300 °C	*(3a)*	16	50—52/12
				(4a)	5.4	58—60/11
(1b)	$(CH_3)_2CH$	CH_3	4 h, 320 °C	*(3b)*	73	79—81/15
				(4b)	10	
(1c)	$(CH_3)_2CHCH_2$	CH_3	4 h, 320 °C	*(3c)*	62	89—91/15
				(4c)	5	
(1d)	$(CH_3)_3C$	CH_3	7 h, 320 °C	*(3d)*	15 [c]	79—81/12
(1e)	C_6H_5	CH_3	2 h, 310 °C	*(3e)*	15	156—158/0.8
(1f)	$(CH_3)_2CH$	C_6H_5	4 h, 300 °C	*(3f)*	22	85—87/0.2

[a] All compounds gave correct elemental analyses (partly as perchlorates and picrates).

[b] Ethyl β-acetaminocrotonate was used for the thermolysis. Here the oxazinone *(1a)* formed along with other compounds reacts further to give *(3a)* and *(4a)* so readily that it can not be isolated.

[c] Along with much unreacted *(1a)*.

with electron-rich multiple bonds, the cycloaddition proceeds regiospecifically[1]. The oxazinones *(1)* cannot be converted into pyrimidines by heating with nitriles, thus ruling out this route for the formation of *(4)*. That 1,3-oxazin-6-ones *(1)* can enter into [4+2] cycloadditions also with electron-poor multiple bonds is demonstrated by the reaction of *(1e)* with dimethyl acetylenedicarboxylate (20 min, 200 °C), which affords the pyridinedicarboxylate *(5)* (m.p. 215—217 °C) in 36% yield.

2-Isopropyl-4,6-dimethylpyridine (3b)

4-Methyl-2-isopropyl-1,3-oxazin-6-one *(1b)*[1] (8.4 g) is heated for 4 h at 320 °C (hot-metal bath). The product of thermolysis is extracted with 1 N HCl. The aqueous phase is neutralized with 1 N KOH, extracted with ether, and dried over $MgSO_4$. After removal of solvent the final product is distilled under water-jet vacuum; yield 2.96 g (73%).

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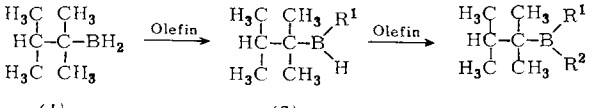
[1] 1,3-Oxazin-6-ones, Part 2.—Part 1: *W. Steglich, E. Buschmann*, and *O. Hollitzer*, Angew. Chem., in press.

[2] *G. L. Cook* and *F. M. Church*, J. Phys. Chem. *61*, 458 (1957).

Reviews

Abstracts of selected progress reports and review articles

Selected partially alkylated boranes have advantages in organic synthesis compared with trialkylboranes, as shown by *E. Negishi* and *H. C. Brown* in a review. Strongly hindered olefins react rapidly to give the monoalkylboranes, of which thexylborane (1,1,2-trimethylpropylborane) *(1)*, prepared from 2,3-dimethyl-2-butene and borane in THF at 0°C, is being used to an increasing extent. Compound *(1)* and olefins react almost quantitatively to form thexylmonoalkylboranes *(2)* which in turn can hydroborate numerous olefins to the mixed trialkylboranes *(3)*. The article considers the use of com-



(1) *(2)* *(3)*

pounds *(3)* for the production of unsymmetrical and cyclic ketones, the coupling of unequal alkyl groups, the synthesis of *trans*-disubstituted olefins, conjugated dienes, diols from dienes, as well as 1,5-diols from monoolefins. Interesting possibilities are presented by selective reduction with *(1)* and with trialkylboranes such as *(3)* which contain the thexyl group. [Thexylborane—A Highly Versatile Reagent for Organic Synthesis *via* Hydroboration. Synthesis *1974*, 77—89; 48 references]

[Rd 703 IE—M]

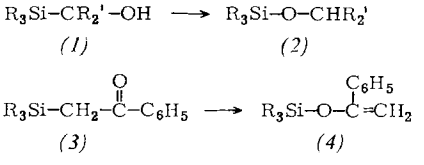
Papers concerning organomagnesium compounds *(1)* which appeared in 1972 are summarized by *C. Blomberg*. The reactions leading to *(1)* are first discussed, followed by the synthesis of halo- and alkoxy-substituted *(1)* and derivatives of *(1)* containing C=C double bonds and other metals; consideration is also given to reactions involving intermediate or "*in-situ*" Grignard compounds. NMR studies on the physical properties, structure, and molecular association of *(1)* are also reported, as are the mechanisms of reactions of *(1)* with *e.g.* carbonyl compounds and free-radical reactions of *(1)*. Many of the papers cited are devoted to reactions between *(1)* and organic compounds, O_2, O_3, peroxides, S, and Te, as well as compounds of B, Si, P, S, and As. [Magnesium. Annual Survey Covering the Year 1972. J. Organometal. Chem. *68*, 69—219 (1974); 368 references]

[Rd 704 IE—M]

Advances in the chemistry of germanium in 1972 are surveyed by *B. C. Pant*. After an overview of the direct syntheses of Ge compounds, the author discusses alkylations and arylations (Grignard method, aryl-Li compounds as intermediates), Ge—H, and Ge-metal compounds (*e.g.* organogermanyl-Hg and -Cd derivatives, germanyl-substituted ferrocenes, and Ge, Ge—N, Ge—P, Ge—As, Ge—O, Ge—S(Se, Te) compounds containing Ti, Zr, Hf) with regard to their synthesis and reactions. Addition of organohydridogermanes to alkynyl derivatives leads to alkenyl and alkynyl compounds. Cyclic Ge compounds can be prepared from multiply unsaturated compounds and organohydridohalogermanes, by addition of $GeCl_2$ to dienes and trienes, and of GeL_2 to alkynes, and *via* silicon compounds. The survey closes with references to Ge-containing polymers and sections on physicochemical and spectroscopic studies and analysis and applications of organogermanium compounds. [Germanium. Annual Survey Covering the Year 1972. J. Organometal. Chem. *68*, 221—293 (1974); 300 references]

[Rd 707 IE—M]

Rearrangements of organosilicon compounds are reviewed by *A. G. Brook*, who devotes particular attention to rearrangements of compounds which have functional groups (OH, C=O, S→O, C=N, *etc.*) attached to the carbon adjacent to silicon. For instance, in the presence of active metals, organometallic compounds, or bases such as pyridine, trialkyl- and triarylsilylmethanols *(1)* undergo intramolecular 1,2 rearrangement to alkoxysilanes *(2)*. The configuration at the Si atom is

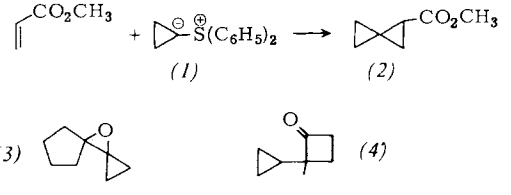


(1) *(2)* *(3)* *(4)*

retained. The article also considers thermal decarbonylation of silanecarboxylic acids and their esters, photolysis of acylsilanes in CCl_4 to give halosilanes, and the thermolysis of β-oxosilanes *(3)* to form alkenyloxysilanes *(4)*. [Some Molecular Rearrangements of Organosilicon Compounds. Accounts Chem. Res. *7*, 77—84 (1974); 59 references]

[Rd 708 IE—L]

New methods of alkylation have been compiled by *B. M. Trost*. Sulfur ylides of type *(1)* have proved to be excellent alkylation



(1) *(2)*

(3) *(4)*

reagents. They react with α,β-unsaturated ketones and esters to give spiropentanes *(2)*, and with aldehydes or ketones to yield oxaspiropentanes *(3)* and/or cyclobutanones *(4)*. Further reactions of these products furnish, *e.g.*, four-, five-, and six-membered carbocycles, γ-butyrolactones, and acyclic compounds of numerous types. [New Alkylation Methods. Accounts Chem. Res. *7*, 85—92 (1974); 47 references]

[Rd 709 IE—L]

New applications of periodic acid and periodates in organic chemistry and biochemistry are reported by *A. J. Fatiadi*. A discussion of various properties of H_5IO_6 and $NaIO_4$ and the mechanism of oxidation by these compounds, which has still not been completely elucidated, is followed by an account of their use as oxidants for polycyclic aromatic hydrocarbons (oxidative dimerization, quinone formation, oxidative hydrol-

ysis), non-benzenoid aromatic compounds, cyclopolyenes (azulene, ferrocene), and steroids, as well as the oxidative degradation of bile pigments, heterocyclics (indole and tryptophan type), and terpenes. Examples of arene iodination by H_5IO_6 or I_2/H_5IO_6 are also presented. Periodates with organic cations are valuable agents for oxidations in aqueous and non-aqueous media. Periodate oxidation can be exploited in the synthesis of heterocyclics, and plays a significant role in stereospecific asymmetric syntheses of carbohydrates. Periodate serves as co-oxidant in oxidations with $KMnO_4$, OsO_4, RuO_4, CrO_3, *etc.* Oxidations of hydroxyaromatics are of preparative value. Typical applications in biochemistry include structural analyses of nucleic acids, and the degradation of collagen, glycoproteins, and carbohydrates. Recent analytical applications of periodates are also reported. [New Applications of Periodic Acid and Periodates in Organic and Bio-Organic Chemistry. Synthesis *1974*, 229—272; 592 references]

[Rd 710 IE—M]

Patents

Abstracts of selected "Deutsche Offenlegungsschriften" (DOS), *i. e.* provisionally published specifications as filed with the German Patent Office

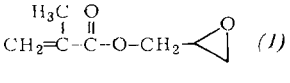
Polyolefin blends with high resistance to low temperatures and to cracking under load consist of a) 20—80 wt.-% of a polypropylene with a viscosity of 4—9 dl/g and b) 80—20 wt.-% of a polyethylene with a viscosity of 0.5—3 dl/g and a density of 0.95—0.97 g/cm³. The component (a) may be modified with 1—20 wt.-% of ethylene, and the component (b) with 1—3 wt.-% of propylene. The blends can be used for injection molding or blow molding. [DOS 2208265; Montecatini Edison S.p.A., Milan]

[PR 162 IE—A]

Non-gelling, water-dispersible cationic epoxy resins for coating compositions that can be deposited electrophoretically on cathodes contain chemically bonded quaternary phosphonium or sulfonium groups. Acids having dissociation constants higher than 1×10^{-5}, such as boric acid or lactic acid, are used as counterions. The resins are prepared *e. g.* from commercial epoxy resins and tributylphosphane in the presence of lactic acid. Coatings formed with these cationic electrophoretic lacquers are more resistant to alkalis and acids than binders that can be deposited anionically. [DOS 2261804; PPG Industries, Inc., Pittsburgh, Pa. (USA)]

[PR 189 IE—W]

High-setting polyacrylate molding powders that can be molded into products having a high elongation at break, tensile strength (1100—2100 kg/cm²), and glass transition temperature (90 °C) consist of a prepolymer of glycidyl methacrylate *(1)*, methyl methacrylate, and methacrylonitrile or acrylonitrile. The readily fusible prepolymers have average molecular

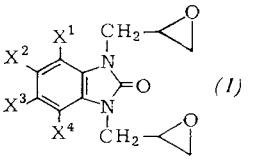


(1)

weights of 2000—10000 (vapor pressure osmometer). The powders are crosslinked for 30 minutes with dibasic acids such as azelaic acid, adipic acid, pentanedicarboxylic acid, sebacic acid, *etc.*[1] at temperatures around 190 C. [DOS 2261314; Ford-Werke AG, Köln]

[PR 191 IE—W]

New diglycidylbenzimidazolones that can be used for the production of casting resins, sintered powders, or molding compositions by curing with amines or anhydrides correspond to the formula *(1)*, where X is preferably a methyl group or hydrogen, or X^1 and X^2 together form a fused benzene ring. The starting compounds are benzimidazolones, which



(1)

are converted into the diepoxide by conventional methods with epichlorohydrin. Cured compositions possess outstanding stability to water. [DOS 2300010; Ciba-Geigy, Basel (Switzerland)]

[PR 192 IE—W]

A process for the production of synthetic paper consists in brief initial treatment of a biaxially drawn film of a high-impact styrene resin/elastomer blend of the ABS type with a solvent that has a swelling action on the styrene polymer, followed by passage of the film through a non-solvent. One obtains a synthetic paper that exhibits excellent writability and printability with a smooth surface. The high-impact blend contains 3 to 7 wt.-% of an elastomer of polybutadiene, polybutadiene-styrene, or an ethylene-propylene terpolymer with an average particle diameter of 0.5 to 5 µm. An acrylonitrile-butadiene-styrene polymer, a methyl methacrylate-styrene-butadiene copolymer, or an acrylonitrile-butadiene-styrene-methyl methacrylate copolymer may also be used as the resin phase (styrene polymer). Examples of solvents that have a swelling action are acetates, ketones, aromatic hydrocarbons, and cyclic ethers; non-solvents are alcohols (C_1—C_{10}). [DOS 2240764; Sumitomo Chemical Co. Ltd., Osaka (Japan)]

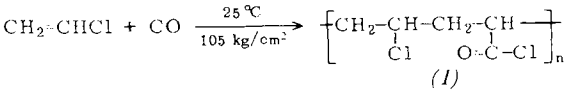
[PR 193 IE—W]

A continuous process for the carbanionic block polymerization of butadiene and styrene makes use of the influence of thorough mixing or of plug flow on the block structure. The monomers of the butadiene type are first continuously polymerized with butyllithium in toluene, with ideal mixing, up to a conversion of 70 % to form a "living" block; again under steady conditions (ideal mixing), styrene is then added in a second stage with continuous flow-through, whereupon a random butadiene-styrene copolymer grows on the butadiene block. The conversion based on butadiene is now 95 %. In a reactor without appreciable back-mixing with plug flow, the styrene first polymerizes with the remaining 5% of butadiene, and styrene then grows on the chain ends. In a subsequent pin mixer, the molecular weight of the living block copolymer can be doubled by introduction of *e. g.* 1,2-dibromoethane. In the resulting block copolymer, $(B)_x$—$(B/S)_y$—$(B/S)_z$—$(S)_n$ (B = butadiene, S = styrene), the first $(B/S)_y$ block has a random structure, and the second $(B/S)_z$ block is "blurred". [DOS 2111966; Badische Anilin- & Soda-Fabrik AG, Ludwigshafen]

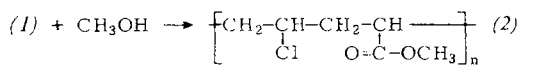
[PR 194 IE—W]

[1] The crosslinking with the corresponding acid (poly)anhydrides is claimed in DOS 2261335 (Ford-Werke AG, Köln).

Copolymers *(2)* **of vinyl chloride and acrylic ester units** can be prepared by free-radical copolymerization of vinyl chloride with carbon monoxide in the presence of an alcohol. A vinyl chloride-acryloyl chloride copolymer *(1)* is first formed, and



(1)

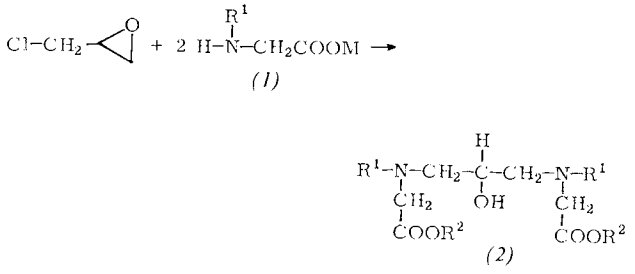


(2)

this reacts further with the alcohol to form *(2)*. [DOS 2211380; Montecatini Edison, S. p. A., Milan (Italy)]

[PR 195 IE—W]

Chelate-forming amino acids having the formula *(2)* are formed as their alkali metal salts from aqueous solutions of amino compounds *(1)* by reaction with epichlorohydrin



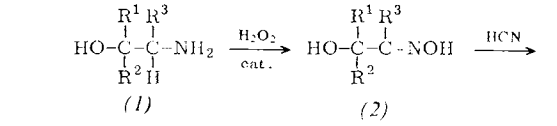
(2)

R^1 = alkyl (C_1–C_{20}), H, CH_2CH_2OH, CH_2COOH, or CH_2COOM; R^2 = H or M; M = alkali metal

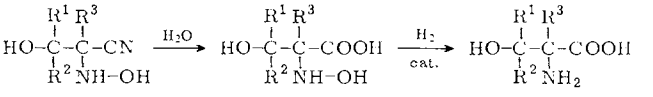
at pH 6—10.5 and at 65—105 C. The free acids can be obtained by acidification to pH 1.3—2. The alkali metal salts of *(2)* are extremely suitable for the complexing of nickel, copper, zinc, and iron ions. The nickel, copper, and zinc complexes can be used for the control of the metal ion concentration of electroplating baths. Zinc and iron complexes are suitable for the supply of complexed zinc and iron to growing plants. The tetracarboxylic acid *(2)*, $R^1 = CH_2COOH$, $R^2 = H$, can be used as a stabilizer for developers in color photography. [DOS 2234905; W. R. Grace & Co., New York (USA)]

[PR 201 IE—D]

β-Hydroxy-α-amino acids *(5)* can be prepared in a four-step process from the amino alcohols *(1)*. The process can be advantageously used *e.g.* for the synthesis of serine from



(1) *(2)*



(3) *(4)* *(5)*

R^1, R^2, R^3 = H or substituted or unsubstituted aliphatic, aromatic, cycloaliphatic, or heterocyclic residues containing 1—8 C atoms

aminoethanol (yield 58%). [DOS 2326874; Snam Progetti S. p. A., Milan (Italy)].

[PR 202 IE—D]

BOOK REVIEWS

Römpps Chemie-Lexikon (Römpp's Lexicon of Chemistry). By *O.-A. Neumüller*. Franckh'sche Verlagshandlung, W. Keller & Co., Stuttgart 1973. 7th Edit. Vol. 2, D—G, 625 pp. + 18 p. Appendix, 215 figures, bound DM 125.—, ISBN 3-440-03852-1; Vol. 3, H—L, 659 pp. + 19 p. Appendix, 170 figures, bound DM 125.—, ISBN 3.440-03853-X.

The publication of the first volume of the fully revised and expanded "Römpp" (to appear in 6 volumes instead of 4) was announced in October 1972[1]. Volumes 2 and 3 (letters D—G and H—L), which were edited under the direction of *O.-A. Neumüller* with the assistance of *K. Esser* and *K. Siekmann*, have now been published. The editors have set themselves the ambitious target of completing the 7th edition, for which a file of more than 160000 cards will have to be dealt with, by 1975 at the latest. It is their intention that none of the entries from the 6th edition should be incorporated into the 7th edition without revision, and that new terms from the current literature should be included at the same time. On browsing through the volumes, in fact, one finds frequent references to works published in 1972 and even 1973 to allow further reading on the problem in hand. In most cases, however, sufficient information is given in the text under the entries. The explanations of the entries are clear and understandable. Special care has been taken to follow the IUPAC nomenclature in the naming of chemical substances. However, this does not mean that older names that are still in common use, such as *Kaliumsulfhydrat* and *Kaliumsilicofluorid* are omitted.

Many new terms are included in the 7th edition. For example, on leafing through one finds HMO theory, hot melts, INDOR, jogs, and KWIC index. Some entries already found in the 6th edition, such as Insecticides, have been considerably expanded. Valuable references are made to recent commercial products, suggesting that catalogs and brochures have been carefully monitored and sifted. The care with which the volumes published so far have been edited, composed, corrected, and printed is commendable.

There is no doubt that chemists will find the new "Römpp" valuable in their daily work. However, it can also be warmly recommended to workers in neighboring fields.

Christian Weiske [NB 198 IE]

[1] Cf. Angew. Chem. internat. Edit. *11*, 947 (1972).

Physikalische Organische Chemie (Physical Organic Chemistry). Reaction Rates, Equilibria, Mechanisms. By *L. P. Hammett*. Verlag Chemie, Weinheim 1973. viii, 413 pp., numerous figures and tables, bound DM 59

More than 30 years ago, *L. P. Hammett* gave an enure field a name and a direction in his book "Physical Organic Chemistry", which has now become a classic. In the present work,

a translation of the 2nd edition, which has little but its name in common with the first, the doyen offers a refreshingly unconventional presentation of the principles underlying the investigation of heterolytic reactions of organic compounds in solution. Established views are very carefully and critically spot-lighted, and their historical development is traced (only apparently loosely) with the intimate familiarity of one who was actually present. At an advanced level (mastery of algebraic details and knowledge of current physicochemical laws are assumed), *Hammett* fills a gap, particularly noticeable in Germany, between textbooks on mechanisms of organic reactions and "pure" physical chemistry.

The work can be broadly divided into three parts. After introductory original remarks on the self-assessment of the chemist, the first part deals with fundamental physicochemical concepts. A self-consistent, very formal and terse description of "Thermodynamics in Solutions" and notes on statistical mechanics are followed by a very useful introduction to the treatment of kinetic data and an excellent account of the theory of the transition state and its direct consequences, such as isotope effects, the Curtin-Hammett principle, *etc.* In the middle part, the author presents a skillful and even exciting illustration of the knowledge that has been acquired, taking as his examples "Nucleophilic Substitution" and "Azo Coupling", and leading the reader naturally to the ion-pair concept, which becomes the central theme in the subsequent chapter "Salt Effects" and "Influence of the Solvent on Reactivity". The final part presents brilliant summaries of fields that are closely associated with the name *Hammett:* acidity functions; acid and base catalysis; linear free energy and isokinetic relations.

This work must inspire all who are interested in the investigation of organic reaction mechanisms. Advanced students should find the chapters on kinetics, theory of the transition state, and linear free energy relations extremely valuable. The layout of the book is very clear, and it contains many excellent graphs. The translation by *Peter Schmid* is good, and a number of technical terms used rather loosely by the author have been discreetly corrected.

Günter Helmchen [NB 200 IE]

Der Umfang des Stoffschutzes für chemische Erfindungen (The Scope of Substance Protection for Chemical Inventions). By *B. Geissler*. Carl Heymans Verlag KG, Cologne—Berlin—Bonn—Munich, 1972. 1st Edit., xxiii, 189 pp., DM 42.

The lifting of the ban on product protection has raised a number of problems, including the question of the scope of product protection for chemical compounds. The subject is discussed systematically and in the light of different legal backgrounds. After an introductory chapter on the history of product protection in Germany, the author deals with the scope of protection provided by product claims for chemical inventions in France, in the USA, and in the Scandinavian countries. After a brief outline of patent theories it is deduced, with a careful weighing up of the arguments for and against absolute product protection, that only a purpose-linked product claim is adequate for chemical inventions. Although this result appears virtually only as a conclusion from the arguments presented, it leaves a certain uneasiness. Perhaps this is because the discussion of the problem of protection for products that have not been prepared chemically, which has long been practiced in the Federal Republic of Germany is a little too brief. Claims of the "agent for..." type that were customary even before the ban on product protection was lifted are purpose-linked (and therefore largely satisfy the author's requirements) but they are incapable of completely satisfying the requirements. If broad product protection is granted to alloys, glasses, and compositions of matter, similar protection should be extended to new chemical substances. The question of whether it is only "apparently" broad would have to be investigated in all cases on the same principles. However, it must not be overlooked that, for example, intermediates cannot be adequately covered by purpose-linked product claims. The "object" problem in the case of new products, with which the author deals, also offers much food for thought: in the discovery of a new substance, does not the essence of the invention after all lie in the provision of this newly constituted substance, as is stated in the Imidazoline Decision of the Federal Supreme Court published after the book went to press? The fact that these new substances must (also) be useful is a legal requirement for patentability. In spite of these misgivings the book can be recommended to anyone who has to deal with the scope of claims: it is a point in favor of a book if it makes the reader think.

Friedrich Rämisch [NB 203]

Dielectric and Related Molecular Processes, Vol. 1. Specialist Periodical Reports. The Chemical Society, London 1972. 1st Edit., xv, 394 pp., several figures and tables, bound £ 8.

In seven chapters the present book contains several up-to-date articles on dielectrics and molecular processes in the substances.

Chapter 1, "The Theory of the Macroscopic Properties of Isotropic Dielectrics" by *B. K. P. Scaife*, presents an introduction from the classical standpoint. Chapter 2, "Dielectric Relaxation and Molecular Correlation" by *G. Wyllie*, deals with the dielectric relaxation processes and the molecular models used for their interpretation. This is probably the most detailed modern review of this field in existence at the moment.

Chapter 3, "Dielectric Polarization in Gases" by *H. G. Sutter*, is concerned with the special problems that arise in the dielectric polarization of gases. Relaxation phenomena are not discussed. Chapter 4, "Time Domain Methods" by *A. Suggett*, gives an excellent, concise (18 pp.) survey of the modern methods in which the pulse technique is used for the determination of dielectric data in liquids, solutions, and polymers.

Chapter 5, "Dielectric Properties of Water and of Aqueous Solutions" by *J. B. Hasted*, deals fairly comprehensively with the phenomena that occur in water or in aqueous solutions, and the structure of water is also discussed. Chapter 6, "Dielectric Polarization Phenomena in Biomolecular Systems" by *G. Schwarz*, presents a brief description (26 pp.) of the use of dielectric methods for the investigation of biopolymers, and the author also deals with his own field, the conformational transitions of biopolymers.

Chapter 7, "General Molecular Theory and Electric Field Effects in Isotropic Dielectrics" by *S. Kielich*, occupies roughly half of the book and gives a detailed account of the electrical and magnetic properties of molecular systems, with special consideration of multipoles and the corresponding potentials. The statistical and electromagnetic properties of dielectrics are then briefly discussed. A very long section is devoted to electro-optical properties, particularly to the Kerr effect, and another section deals with the changes in the electrical properties in strong electric fields.

Despite its heterogeneous content, the book will be of great value to any scientist working in the field of dielectrics. It

is regrettable that apart from the section on biopolymers, the dielectric phenomena of high polymers are not discussed. The book also lacks descriptions of measurements in the microwave and far IR regions. It is to be hoped that these topics will be included in subsequent volumes of this series.

Werner Zeil [NB 204 IE]

Biosynthesis, Vol. 1. Specialist Periodical Reports. The Chemical Society, London 1972. 1st Edit., 149 pp., bound £ 6.50.

The present first volume in a series on the biosynthesis of cell constituents is mainly concerned with methodological studies and results for natural products from plants. The literature discussed is mainly from the years 1970 and 1971, though earlier studies are also included where these are required to clarify relationships and basic principles.

The general principles are presented by *S. A. Brown* in the opening chapter on labeling procedures in living plants and in isolated tissue systems, with mutants and with specific antimetabolites. This chapter also deals with the recent development of differential NMR spectroscopy for following the fate of structural components, which can take the place of isotope studies in favorable cases. The book then continues with the discussion of fields in which particularly fruitful and penetrating developments and results have been achieved in recent years: the biosynthesis of monoterpenes and sesquiterpenes from acetyl coenzyme A (*J. R. Hanson*), the conversion of isopentenyl pyrophosphate into triterpenes, steroids, and carotenoids (*H. H. Rees* and *T. W. Goodwin*), and the biogenesis of phenolic compounds from shikimic acid or from acetate units (*J. B. Harborne*). One still often has to resort to general feeding experiments here to determine the reaction sequence; in the case of the flavonoids, however, it has been possible to establish the individual enzymatic steps, particularly through the work of *Grisebach*, and it is to be expected that the next volume will be able to report similar progress from other synthetic chains of plant materials. The book ends with a mainly tabular summary of the biogenesis of alkaloids (*E. Leete*), a complete account of which is to be given in another series.

The detailed studies on the stereochemical course of the condensations, rearrangements, and oxidoreductions in the polyprene syntheses are conceptionally and experimentally outstanding. The individual chapters are excellently written, and not only give the essential lines of current research but also show the directions that are now becoming important. The careful selection and discussion of the literature makes the volume a strongly commendable guide to these publications on plant physiology, which are often widely scattered and not readily accessible. Those who are working in the field will find this helpful in their own work, and it will also prove an excellent aid to anyone seeking a general survey. These volumes thus really fulfill their intended purpose, and will be welcomed by everyone concerned with the biochemistry of the natural products of plants.

L. Jaenicke [NB 205 IE]

Atom-Absorptions-Spektroskopie (Atomic Absorption Spectroscopy). By *Bernhard Welz*. Verlag Chemie GmbH, Weinheim/Bergstr. 1972. 1st Edit., x, 216 pp., 52 figs., 46 tables, cloth DM 58.—.

Atomic absorption spectroscopy is one of the methods of instrumental analysis whose widespread use is not confined to chemical laboratories. Atomic absorption spectrometers are nowadays to be found in many biological, mineralogical, and clinical laboratories. This spectroscopic method is also one of the standard methods of analysis in the protection of the environment. When an instrumental method of analysis is used in such a wide variety of fields, one often finds that it is not always used to its full advantage, mainly because of the user's training. A particularly welcome feature of the present book, therefore, is that it has been written in such a way that it will also be understandable to biologists, mineralogists, geologists, and clinical chemists.

The book deals with the physical principles of the method without going into special physical and mathematical details, as well as with the component parts of the instrument (light sources, optics, electronics, *etc.*) and the determination of the various elements (in alphabetical order).

A separate chapter is devoted to specific applications in medicine, biochemistry, toxicology, food chemistry, geochemistry, petrochemistry, *etc.* Literature references for further information are given here in tables arranged according to elements for the particular type of test sample in question (*e.g.* serum, urine, fertilizer, *etc.*). The book also contains a short chapter on flame emission spectroscopy and atomic fluorescence spectroscopy, a very comprehensive bibliography (859 references), and an appendix listing the commercially available atomic absorption spectrometers (with tables of technical details).

The book, which may be described as an excellent synthesis of introduction and reference work, will be useful to anyone who is concerned with atomic absorption spectroscopy.

Egon Fahr [NB 207 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal.

Wechselwirkung von π-Elektronensystemen mit Metallhalogeniden. By *H.-H. Perkampus*. From the series "Molekülverbindungen und Koordinationsverbindungen in Einzeldarstellungen". Edited by *G. Briegleb*, *F. Cramer*, and *H. Hartmann*. Springer-Verlag, Berlin 1973. xi, 215 pp., bound DM 68.—.

Contents: Einleitung und Abgrenzung; Donatoren und Acceptoren; Proton-Additions-Komplexe; π-Komplexe; σ-Komplexe.

Free-Radical Chemistry. Structure and Mechanism. By *D. C. Nonhebel* and *J. C. Walton*. Cambridge University Press 1974. xv, 571 pp., bound £ 15.00.

Contents: Production of Free Radicals; Detection; Shapes; Stabilities; Reactions in the Gas Phase; Reactions of Atoms; Alkyl Radicals; Heteroradicals; Oxidations and Reductions; Aromatic Substitution; Fragmentations; Rearrangements; Cyclizations; Displacement Reactions.

An Introduction to Solid State Physics and its Applications. By *R. J. Elliott* and *A. F. Gibson*. Macmillan, London 1974. xxi, 490 pp., bound £ 5.95.

Contents: Crystal Structure; Excitations; Lattice Vibrations; Electrons in Bands; Imperfections in Crystals; Optical Properties of Solids; Optical and Microwave Properties of Free Carriers; Transport; Semiconductor Junction Devices; Magnetism.

Biosynthesis, Vol. 2. Senior Reporter: *T. A. Geissman*. The Chemical Society, London 1973. ix, 308 pp., bound £ 8.00.— A volume in the series "Specialist Periodical Reports".

Handbuch der photometrischen Analyse organischer Verbindungen, Bd. 1 und 2. By *B. Kakáč* and *Z. J. Vejdělek*. Verlag Chemie GmbH, Weinheim 1974. Together viii, 1309 pp. bound DM 320.—.

Faraday Discussions of the Chemical Society, No. 2: Solid/Solid Interfaces. Issued by the Chemical Society, London, The Faraday Division 1972. 228 pp., stitched £ 5.00.

Diatomic Interaction Potential Theory. Vol. 1: Fundamentals. By *J. Goodisman*. From the series "Physical Chemistry". Academic Press, New York 1973. xiii, 299 pp., bound $ 24.00.

Contents: Potential Curves; Potential Energy Curves; Methods of Calculation.

Structure and Bonding, Vol. 16: Alkali Metal Complexes with Organic Ligands. Edited by *J. D. Dunitz et al.* Springer-Verlag, Berlin 1973. 189 pp., stitched DM 56.—.

Contents: Organic Complexing Agents; Complexes with Alkali Metal Ions; Complexing Agents in Membranes; Thermodynamics of Cation-Macrocyclic Compound Interaction.

Structure and Bonding, Vol. 15: Coordinative Interactions. Edited by *J. D. Dunitz et al.* Springer-Verlag, Berlin 1973. 189 pp., stitched DM 56.—.

Contents: Ronald Nyholm; Metal Complexes of Olefin-Group; V Ligands; Structural Radii, Electron-cloud Radii, Ionic Radii and Solvation; Donor-Acceptor Interactions; Redox Properties; Stepwise Formation of Metal-Ion Complexes in Aqueous Solution.

Röntgenstrukturanalyse organischer Verbindungen. Eine Einführung. By *G. Habermehl, S. Göttlicher*, and *E. Klingbeil*. Vol. 12 of the series "Anleitungen für die chemische Laboratoriumspraxis". Edited by *F. L. Boschke*. Springer-Verlag, Berlin 1973. xii, 268 pp., bound DM 76.

Contents: Kristallographische Grundlagen; Beugung von Röntgenstrahlen; Aufnahmeverfahren; Fourier-Reihen; Absolutbestimmung der Strukturamplituden; Symmetriezentrumtest; Wilson Statistik; Phasenbestimmung der Strukturamplituden; Verfeinerung der Lage- und Schwingungsparameter.

Techniques of Combined Gas Chromatography/Mass Spectrometry: Applications in Organic Analysis. By *W. H. McFadden*. John Wiley & Sons, New York 1973. 463 pp., bound £ 9.50

Contents: Components of a Mass Spectrometer; Fundamentals of Gas Chromatography; Vacuum Technology; GCMS Interface; Operational Techniques; Computer in GCMS; Applications.

Interfinish 1972. Berichtsband des 8. Interfinish Kongresses, Basel, September 1972. Edited by *N. Ibl, K. Oesterle, J. P. Renaud*, and *A. L. Saboz*. Forster-Verlag, Zürich 1973. 460 pp., Sfr. 90.—.

The Interpretation of Proton Magnetic Resonance Spectra. A Programmed Introduction. By *E. R. Haws, R. R. Hill*, and *D. J. Mowthorpe*. Heyden & Son, London 1973. xii, 180 pp., stitched DM 20.50.

Contents: Principles; Chemical Shift and Integration; Spin-Spin Coupling; Complex Spectra; Temperature Dependent Spectra; Geminal Non-Equivalence; Problems.

Solvent Effects on Chemical Phenomena, Vol. 1. By *E. S. Amis* and *J. F. Hinton*. Academic Press, New York 1973. x, 474 pp., bound $ 32.50.

Contents: Introduction; General Concepts of Solvation; Solvation of Ions; Mixed Aqueous Solvent Systems; Solvent Influences on Rates and Mechanisms.

Das Arbeiten mit ionenselektiven Elektroden. By *K. Cammann*. Springer-Verlag, Berlin 1973. From the series "Anleitungen für die chemische Laboratoriumspraxis". Edited by *F. L. Boschke*. xii, 226 pp., bound DM 56.-

Contents: Potentiometrie; Elektrodenpotentialmessung; Ionenselektive Elektroden; Meßtechnik; Analysentechniken; Anwendungsbeispiele.

Pyridazines. Edited by *R. N. Castle*. From the series "The Chemistry of Heterocyclic Compounds". Edited by *A. Weissberger* and *E. C. Taylor*. John Wiley & Sons, New York 1973. ix, 905 pp., bound £ 40.00.

Contents: Physical Properties; Pyridazinones, Alkoxy- and Aryloxypyridazines; Halopyridazines; Aldehydes, Ketones, Alcohols, Carbocylic Acids; Aminopyridazines; Nitropyridazines and Reduction Products (except Amines); N-Oxides; Sulfur Compounds.

Mass Spectrometry of Pesticides and Pollutants. By *S. Safe* and *O. Hutzinger*. CRC Press, Cleveland/USA 1973. 220 pp., bound $ 32.50.

Contents: Introduction to Mass Spectrometry; Halogenated Pollutants; Polycyclic Hydrocarbons; Phthalates; Chlorinated Compounds; Carbamates; Ureas; Anilides; Chloroanilines; Triazines; Uracils; Organometallic Compounds; Organophosphorus Pesticides.

Modern Electrochemistry, Vol. 1. An Introduction to an Interdisciplinary Area. By *J. O'M. Bockris* and *A. K. N. Reddy*. A Plenum/Rosetta Edition, Plenum Publishing Corporation, New York 1973. ix, 622 pp., stitched $ 10.29.

Contents: Ion-Solvent Interactions; Ion-Ion Interactions; Ion Transport in Solutions; Protons in Solution; Ionic Liquids.

Modern Electrochemistry, Vol. 2. An Introduction to an Interdisciplinary Area. By *J. O'M. Bockris* and *A. K. N. Reddy*. A Plenum/Rosetta Edition, Plenum Publishing Corporation, New York 1973. 1432 pp., stitched $ 10.29.

Contents: The Electrified Interface; Electrodics; Electrodic Reactions; Electrochemical Systems of Technological Interest.

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Carbon Suboxide in Preparative Organic Chemistry

New synthetic methods (1)

By Thomas Kappe and Erich Ziegler[*]

Although it has been known for nearly 70 years, carbon suboxide was used almost exclusively for the preparation of simple malonic acid derivatives until about 1960. Since then, however, the significance of this unusual "bisketene" has steadily increased in synthetic chemistry (especially that of heterocyclic compounds). This progress report surveys the possible applications of C_3O_2 in preparative organic chemistry, including photochemical reactions.

1. Introduction

While studying the action of phosphorus pentoxide on diethyl malonate at 300 °C, *Diels*[1] observed that the generation of ethylene and some CO_2 was accompanied by formation of small quantities of another gas which first caught his attention by virtue of its powerful irritating action on the mucous membranes. He was able to isolate a substance having a boiling point of 6.8 °C, to which he assigned[2] the structure of allenedione *(1)*

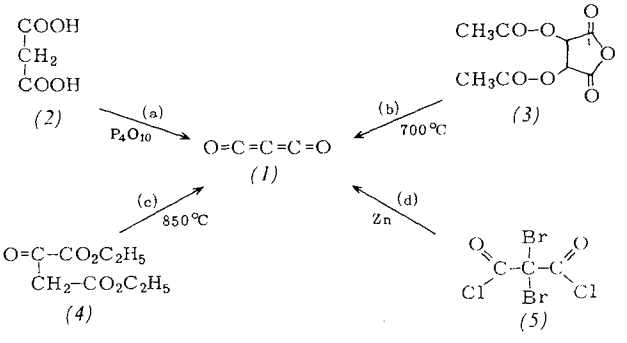
O=C=C=C=O *(1)*

on the basis of elemental analysis, molecular-weight determination, and, above all, a series of reactions leading to malonic acid derivatives. He named the compound "carbon suboxide"[3]. The following year *Diels*[4] published another much more productive synthesis from malonic acid and P_4O_{10} which is still used for the preparation of *(1)* in many laboratories.

The name carbon suboxide for *(1)* is somewhat misleading since the compound does not behave as a "normal" oxide of carbon but as a bisketene. Viewed in this way, *(1)* can be considered as a doubly dehydrated malonic acid; most of its reactions furnish derivatives of this acid. Owing to its unusual structure, carbon suboxide has mainly attracted the interest of theoretical and physical chemists since its discovery. Results of such studies have been presented in a recent review[5]. In the following we shall therefore only briefly touch upon the most recent results concerning the structure of C_3O_2. The aim of this progress report is primarily to present recently developed applications of carbon suboxide to preparative organic chemistry, particularly in the synthesis of heterocyclic compounds[6]

2. Preparation of Carbon Suboxide

Of the many reactions known to afford C_3O_2 there are four which lend themselves to laboratory preparations:



a) Dehydration of malonic acid *(2)* with P_4O_{10} at 140—150 °C, as used by *Diels*[4] (*ca.* 23% yield);

b) Thermolysis of *O,O*-diacetyltartaric anhydride (2,5-dioxotetrahydrofuran-3,4-diyl diacetate) *(3) in vacuo* at 600—700 °C

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(46—68%) or under normal pressure at 770°C (*ca.* 45% yield)[7];

c) Pyrolysis of diethyl oxaloacetate *(4)* in the presence of acetic anhydride at 850—880°C (48% yield)[9]; and

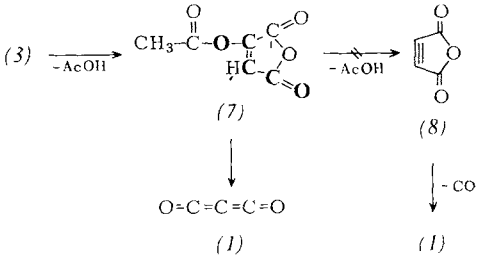
d) Dehalogenation of dibromomalonyl chloride *(5)* with zinc turnings in boiling ether (*ca.* 80% yield)[10, 11].

These preparations are considered in the available reviews[5, 6], in some cases[6e] with diagrams of apparatus. Thermal decomposition of silver ketenide *(6)*, which is accessible from silver acetate and acetic anhydride in pyridine, is also reported to yield compound *(1)* quantitatively and in high purity[12]:

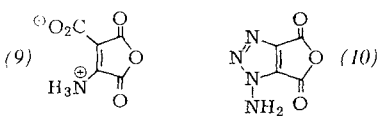
$$\underset{(6)}{2Ag_2C{=}C{=}O} \xrightarrow[150\,^{\circ}C]{} \underset{(1)}{C_3O_2} + C + 4Ag$$

This route does not yet seem to have been exploited in preparative work, probably owing to the danger of explosion of *(6)*.

The most important preparation of *(1)* is that starting from diacetyltartaric anhydride *(3)*. However, until very recently the formation of *(1)* was interpreted erroneously. *Ott*[13], the discoverer of the reaction, initially formulated elimination of acetic acid to give acetoxymaleic anhydride *(7)*, as was later confirmed; further loss of acetic acid was assumed to give acetylenedicarboxylic anhydride *(8)* which undergoes fragmentation with decarbonylation to form *(1)*. In contrast to the results of *Dashkevich*[9] who, in 1960, deduced the intermediacy of the hetaryne *(8)* in formation of *(1)* from both *(3)* and *(4)* on the basis of ^{14}C-labeling studies, in 1968 *Crombie*, *Gilbert*, and *Houghton*[8] unequivocally ruled out *(8)* (or any other symmetrical derivative) as intermediate by application of five differently ^{14}C-labeled diacetyltartaric anhydrides *(3)* and acetoxymaleic anhydrides *(7)* and of *(3)* bearing an ^{18}O label in the ester oxygen function. Instead, C^1 in *(3)* and *(7)* is eliminated and an O atom of the 2-hydroxy group of the original tartaric acid is retained; *i.e.* C_3O_2 arises from the atoms shown in bold print in formula *(7)*[14].



The question whether the hetaryne *(8)* occurs as an intermediate in the pyrolysis of *(3)*, *(4)*, and *(7)* is of significance since in the case of an affirmative answer other methods



of aryne chemistry could be employed in the preparation of *(1)*: *e.g.* diazotization of the anhydride *(9)* or reaction of the aminotriazole *(10)* with lead tetraacetate.

3. Structure of Carbon Suboxide

The geometrical and electronic structure of carbon suboxide has been a subject of detailed study in recent years[15–17]. The question whether C_3O_2 possesses a linear, angled, or zigzag structure[18] seemed to have been definitely answered in favor of a linear geometry on the basis of exact analysis of the IR spectrum[19–22] when in 1969 *Smith* and *Barrett*[23] put forward the hypothesis that C_3O_2 is only a quasilinear molecule, the frequency of the bending mode at the central C atom being 63 cm^{-1}, on the basis of certain peculiarities in the vibrational spectrum. Deflection experiments on molecular beams of C_3O_2 in inhomogeneous electric fields have recently demonstrated that the angle at the central carbon atom can deviate by at most 9° from the linear configuration. Electron diffraction studies[24] on C_3O_2 lead to a similar result.

Recent *ab initio* calculations with geometrical searching by *Sabin* and *Kim*[17] failed to show a low energy barrier for a bending vibration about the central C atom. Instead, a steep energy gradient is found even for small deviations (1°) from the linear structure. According to this calculation[17], the C=C and C=O distances are 1.332 and 1.243 Å (±0.005 Å) respectively [the measured values are ≈1.29 and 1.17 Å][25]; the resulting π-orbital energies are listed in Table 1, together with the *ab initio* results and values calculated by *Siegbahn*[26] from photoelectron spectra.

Table 1. π-Orbital energies [eV] in carbon suboxide *(1)*.

Method	$^1\Pi_u$	$^1\Pi_g$	$^2\Pi_u$
ab initio [17]	−18.66	−17.69	−11.89
ab initio [26]	−18.72	−17.74	−11.12
from ESCA values [26]	−16.0	−15.0	−10.8±0.2

Table 2 shows the charge distribution in carbon suboxide, which is also of significance in its chemical behavior. The unusually high negative charge on the central atom C^2 is surprising. Noteworthy is the good agreement between the values calculated from experimentally determined ESCA

Table 2. Charge distribution in $O{=}C^1{=}C^2{=}C{=}O$ *(1)*.

	O	C^1	C^2
Calc. from			
ESCA values [26]	−0.28	+0.45	−0.33
CNDO/2 [27]	−0.28	+0.46	−0.36
ab initio [17]	−0.260	+0.419	−0.318
ab initio [26]	−0.25	+0.59	−0.68

values[26] and those of a CNDO/2 calculation by *Ohlsen* and *Burnelle*[27] and the *ab initio* calculation by *Sabin* and *Kim*[17]; the *ab initio* values obtained by *Siegbahn*[26] predict an even greater polarization.

4. Reactions of Carbon Suboxide

As doubly dehydrated malonic acid, carbon suboxide *(1)* is extremely reactive. It is therefore hardly surprising that C_3O_2 can be used for reactions which give only unsatisfactory

yields, if they proceed at all, when attempted with other malonic acid derivatives. Many reactions of *(1)* even take place below 0 °C. Moreover, C_3O_2 is a "clean" reagent: viewed formally all the reaction products are adducts of *(1)* to the substrate, *i.e.* the reaction gives no by-products like HCl or chlorinated phenols such as are formed with malonyl chloride or reactive malonic esters[28,29]. The advantage of using *(1)* with sensitive substrates or products is clearly seen. Catalysts such as $AlCl_3$, and H_2SO_4 or *p*-toluenesulfonic acid, can considerably enhance the electrophilicity of *(1)*.

4.1. Reactions with Nucleophiles to Give Open-Chain Malonic Acid Derivatives

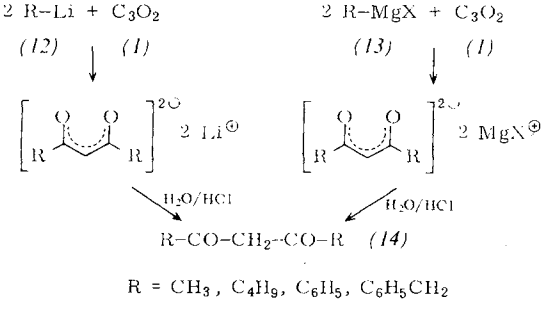
When present in excess, nucleophiles (NuH) such as aliphatic or aromatic amines[6d,6e], alcohols[6d,6e,30], phenols[6d,6e,30], or thiols[30,31] react smoothly with C_3O_2 to form malonamides, esters, or thioesters.

$$\underset{(1)}{O{=}C{=}C{=}C{=}O} + 2NuH \longrightarrow Nu{-}CO{-}CH_2{-}CO{-}Nu$$

Reaction with water is relatively slow (perdeuteriomalonic acid is formed with D_2O[32]). Hence the reaction with amines[33], anilines[34] amino acids[33,35], and proteins[36] can be carried out in buffered aqueous solution. *Hegar*[37] studied the addition of *e.g.* phenol to *(1)* in aqueous solution in the pH range 1—14 at 0 °C. He obtained diphenyl malonate as sole product; the maximum yield was found at pH 11. Alkyl malonate formation is catalyzed not only by acids[30] (enhanced electrophilicity of C_3O_2), but also by the corresponding Na alkoxides (conversion of substrate into the more nucleophilic anion). The yield of ester then becomes almost quantitative[38]. Oximes[6a,39], hydroxylamine and its *N*-substituted derivatives[40], amide oximes[41] and also some of their ethers[42] generally give linear malonic acid derivatives. In some cases, open-chain *N,N'*-diacylmalonamides *(11)* have also been obtained from carboxamides (but not from thioamides, cf. Section 4.3.2)[43].

$$2R{-}CONH_2 + \underset{(1)}{O{=}C{=}C{=}C{=}O} \longrightarrow \underset{(11)}{R{-}CO{-}NH{-}CO{-}CH_2{-}CO{-}NH{-}CO{-}R}$$

Action of excess organolithium compounds *(12)* or Grignard compounds *(13)* on C_3O_2 in ether followed by hydrolysis likewise furnishes β-diketones *(14)*[44,45], sometimes in enolized form.



4.2. Reactions Affording Ketenecarboxylic Acid Derivatives and Acylketenes

Nucleophiles add to C_3O_2 in a stepwise reaction involving ketenecarboxylic acid derivatives such as *(15)*. *Staudinger*[46] discovered in 1912 that, *e.g.* the non-catalyzed reaction of alcohols with *(1)* is slower than with other ketenes, and that unreacted C_3O_2 is still detectable after several days at low temperatures. Relevant quantitative studies have been performed only very recently with the aid of gas chromatography[47,48]. Remarkably, these investigations show (in contrast to previous assumptions[6f]) that the rate constant of the initial step, *i.e.* formation of the ketenecarboxylic acid derivative [*e.g.* the ester *(15)*] is more than double that of the second step in all the cases considered. A relatively high concentration of intermediate must therefore always be expected in reactions of *(1)* with nucleophiles, even when the latter are present in excess. Figure 1 shows the course of addition of 1-propanol to C_3O_2.

$$\underset{(1)}{C_3O_2} \xrightarrow[k_1]{+R{-}OH} \underset{(15)}{ROCO{-}CH{=}C{=}O}$$

$$\xrightarrow[k_2]{+R{-}OH} \underset{(16)}{ROCO{-}CH_2{-}COOR} \qquad k_1 > 2k_2$$

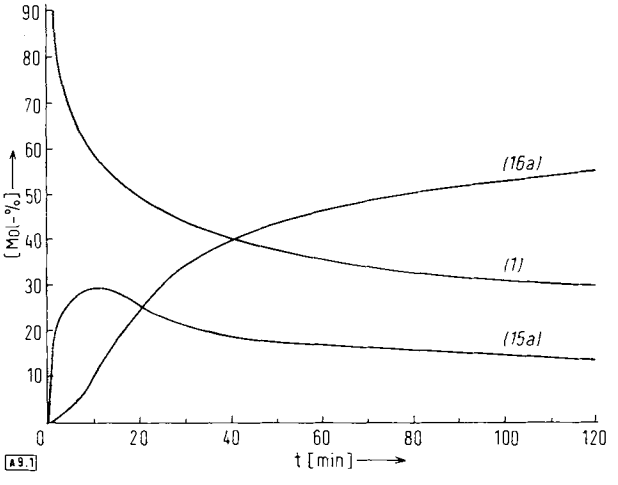


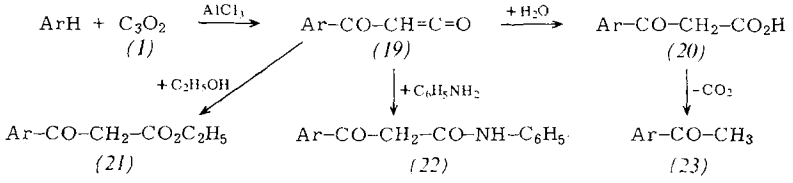
Fig. 1. Plot of reaction of C_3O_2 *(1)* (3.3 mmol) with 1-propanol (10 mmol) in ether (30 ml) at -20 °C (after [48]). Intermediate, *n*-propyl ketenecarboxylate *(15a)*; product, di-*n*-propyl malonate *(16a)*.

The reverse reaction, formation of such ketenecarboxylic acid derivatives as reactive intermediates on thermolysis of malonic esters [*i.e.* *(16)* → *(15)*] was postulated as early as 1955[49,28]. In 1967 *Ziegler* and *Sterk*[50] were able to show in an IR study that heating of malonyl chloride *(18)* to 80 °C affords the same ketenecarbonyl chloride *(17)* as is formed on mixing of gaseous HCl and C_3O_2. Addition of alcohols to *(1)* with formation of *(15)* can likewise be observed by IR spectroscopy whereas cleavage of aryl malonates to ketenecarboxylic esters can only be detected above *ca.* 250 °C by this method[51].

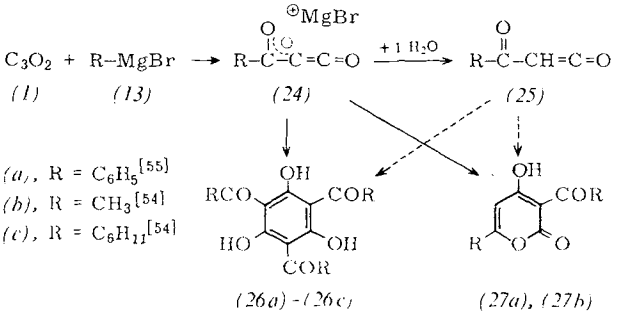
$$\underset{(1)}{C_3O_2} \xrightarrow{+HCl} \underset{(17)}{Cl{-}CO{-}CH{=}C{=}O} \xleftarrow[80\,^\circ C]{-HCl} \underset{(18)}{Cl{-}CO{-}CH_2{-}CO{-}Cl}$$

The intermediate formation of relatively inert ketenecarboxylic acid derivatives or acylketenes in reactions of *(1)* with nucleophiles can be exploited for preparation of mixed-functional

derivatives of malonic acid. Friedel-Crafts acylation of aromatics with C_3O_2 followed by hydrolysis and decarboxylation of the aroylacetic acids *(20)* generally affords only the methyl ketones *(23)*[52]. The existence of the aldoketene *(19)* can however be established by treating the reaction mixture with ethanol or aniline instead of water. In this case, ethyl aroylacetates *(21)* or aroylacetanilides *(22)* are formed[53].



Reaction of the Grignard compounds *(13a)*—*(13c)* with C_3O_2 in the molar ratio 1 : 1 also proceeds *via* the non-isolable acylketenes to yield the 2,4,6-triacylphloroglucinols *(26a)*—*(26c)* as major products; the 4-hydroxy-2-pyrones *(27a)* and *(27b)* can be isolated as side products[54, 55]. In the most thoroughly studied[55] reaction of *(13a)*, formation of acetophenone, β-hydroxy-β,β-diphenylpropionic acid, benzophenone, triphenylmethanol, and biphenyl was also



detected[56]. Most probably, trimerization to the phloroglucinols *(26)* and dimerization to the pyrones *(27)* does not occur *via* the free acylketenes *(25)*, but proceeds directly *via* the corresponding MgBr complexes[55]. While dimerization of acylketenes to 6-substituted 3-acyl-4-hydroxy-2-pyrones of type *(27)* has long been known[57], the trimerization of an aldoketene to a phloroglucinol derivative has hitherto apparently been observed only with benzylketene[58].

4.3. Reactions Yielding Heterocycles

On reaction of C_3O_2 with substances whose molecules possess two nucleophilic centers, ring closures can of course occur *via* the intermediate acylketenes. Prerequisites for such a reaction course are:

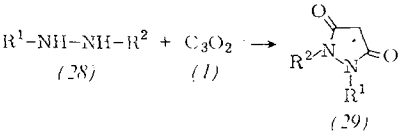
a) A favorable mutual spatial orientation of the two nucleophilic atoms (1,2; 1,3; or 1,4 position, the number of six-membered heterocycles resulting from a 1,3-arrangement so far having been found to greatly outweigh the other possibilities), and

b) approximately comparable nucleophilicity of the two centers (otherwise mainly open-chain products result).

In borderline cases where both open-chain malonic acid derivatives and cyclic products are formed, the yield of the latter should increase on application of the dilution principle (particularly in view of the relatively long lifetimes of the ketenecarboxylic acid intermediates). However, systematic studies on this point have yet to be performed.

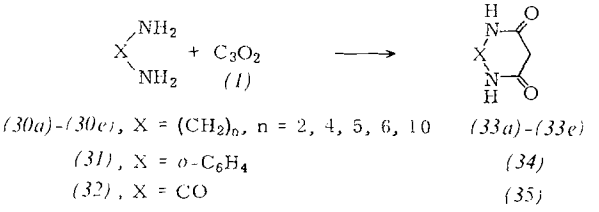
4.3.1. Heterocycles Containing Two N Atoms

The reaction of C_3O_2 with phenylhydrazine yielding 1-phenylpyrazolidine-3,5-dione *(29a)* was described by *Van Alphen*[59] as long ago as 1924. Later reports[60–62] are concerned with reactions of other substituted hydrazines to form pyrazolidinediones, including that of hydrazobenzene *(28b)* which otherwise tends to resist "malonylation". Unsubstituted hydrazine itself gives only linear polymers[61].



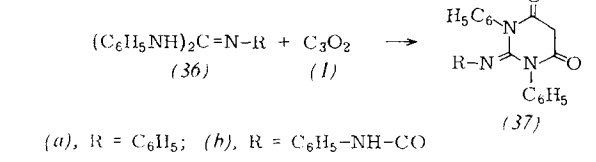
(a), $R^1 = C_6H_5$, $R^2 = H$[59]
(b), $R^1 = R^2 = C_6H_5$[60]
(c), $R^1 = R^2 = CH_3$[61]

Slow introduction of C_3O_2 into dilute ethereal solutions of the aliphatic diamines *(30a)*—*(30e)* furnishes the 7- to 15-membered cyclic malonamides *(33a)*—*(33e)* in quantitative yield[61, 63]. Rapid addition of *(1)* (*e.g.* by shaking of a toluene C_3O_2 solution with an aqueous diamine solution) leads to linear polyamides[37, 64].



(30a)–*(30e)*, X = $(CH_2)_n$, n = 2, 4, 5, 6, 10 — *(33a)*–*(33e)*
(31), X = *o*-C_6H_4 — *(34)*
(32), X = CO — *(35)*

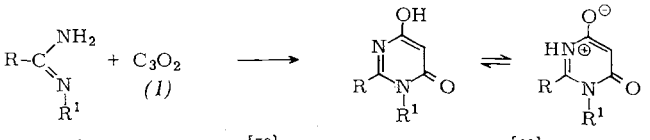
o-Phenylenediamine *(31)* gives 1*H*-1,5-benzodiazepine-2,4(3*H*,5*H*)-dione *(34)*[59], and urea *(32)* smoothly yields barbituric acid *(35)* (75% in acetone + $AlCl_3$[61], 85% in DMF[65]). While reaction of diphenylguanidine affords two isomeric 2-iminobarbituric acids alongside an open-chain malonic acid derivative, the threefold substituted guanidines *(36a)* and *(36b)* give only the 2-iminobarbituric acids *(37a)* and *(37b)* respectively[66].



(a), R = C_6H_5; *(b)*, R = C_6H_5–NH–CO

Amidines *(38)* react with malonic esters in the presence of Na alkoxide[67] or with malonyl chloride[68] to give moderate

yields of hydroxypyrimidones *(39)*[69]; however, as a cyclizing reagent, carbon suboxide leads to almost quantitative conversion even in the cold. Especially good results are obtained with *N*-aryl-substituted benzamidines[70] (cf. also Section 4.3.5.2).



(38), R^1 preferably Ar[70]

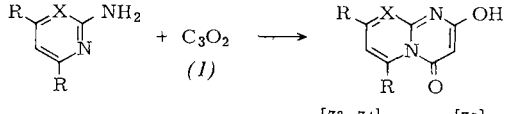
(39)[69]

(40), R = C_6H_5, CH_3; R^1 = OC_2H_5, $OCH_2C_6H_5$[42, 71]

(41)

Amide oxime ethers react with malonyl chloride to give exclusively pyranopyrimidinediones[71]. Experiments on acetamide oxime ether and benzamide oxime ether *(40)*, however, showed that the parent compounds, in this case the *N*-alkoxypyrimidones *(41)*, are also accessible by reaction with C_3O_2 at -20 °C[42, 71].

α-Amino-N-heterocycles such as 2-aminopyridines, -pyrimidines, -oxazoles, -thiazoles, *etc.* can be regarded as cyclic amidines. It therefore comes as no surprise that substances of this class undergo exceptionally ready reaction with C_3O_2 to give fused hydroxypyrimidones, some of which are accessible only with difficulty, if at all, by other routes. Thus 2-aminopyridine *(42a)* furnishes "malonyl-α-aminopyridine" *(43a)*[73–75] which was first synthesized by *Chichibabin* in 1924[72]. The 2-aminopyrimidines *(42b)* and *(42c)* likewise afford almost quantitative yields of the pyrimidopyrimidines *(43b)* and *(43c)* respectively[43]. A more complicated reaction course is observed in the cyclization of non-symmetrically substituted 2-aminopyrimidines for which ring closure can adopt two different directions, depending upon the substituent[76].

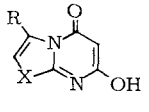


(42) *(a)*, X = CH, R = H[73, 74]

(b), X = N, R = H[43]

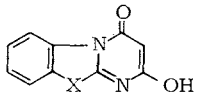
(c), X = N, R = CH_3[43]

(43)[75]



(44), X = O, R = H (100%)[77]

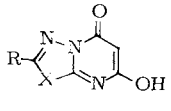
(45), X = S, R = H (90%)[43]; R = Alk, Ar (53–58%)[78]



(46), X = O (89%)[74, 77]

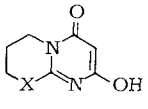
(47), X = S (83%)[74, 78]

2-Aminooxazole and 2-aminothiazole react similarly to form the fused pyrimidines *(44)*[77] and *(45)*[43, 78] respectively. 2-Aminobenzoxazole and 2-aminobenzothiazole yield *(46)*[74] and *(47)*[74, 78], respectively. Reaction of 2-amino-1,3,4-oxadiazole and 2-amino-1,3,4-thiadiazoles with *(1)* gives *(48)*[74]



(48), X = O, R = H (67%)[74]

(49), X = S, R = H, Alk, Ar (87–96%)[74, 79]



(50), X = O (100%)[77]

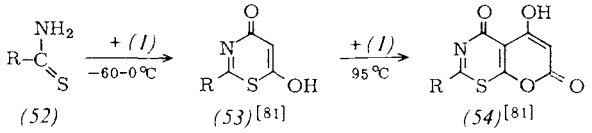
(51), X = S (92%)[77]

and compounds *(49)*[74, 79], respectively. Finally, *(50)* and *(51)* respectively can be obtained from 2-amino-5,6-dihydro-4*H*-1,3-oxazine and -thiazine[77].

4.3.2. Heterocycles Containing One N and One S Atom

As mentioned in Section 4.1, carboxamides yield only open-chain malonic acid derivatives with C_3O_2[43]. Owing to the approximately comparable nucleophilicity of their N and S atoms, thioamides *(52)* behave differently. Thus thiobenzamide[43] and substituted thiobenzamides give almost quantitative yields of 6-hydroxy-1,3-thiazin-4-ones *(53)* at as low a temperature as -60 °C[65, 80–82]. Heterocyclic thioamides like nicotinthioamide, isonicotinthioamide, and picolinthioamide behave similarly[43, 65].

On use of an excess of C_3O_2 and at higher temperatures, further reaction with *(1)* occurs. Pyrone derivatives *(54)* are easily isolated in pure form, whereas higher polypyrones can only be obtained as mixtures (cf. also Section 4.6)[43, 65]. Addition of *ca.* 15 C_3O_2 molecules (statistical average) could be detected with a product that was insoluble in boiling dioxane[43].

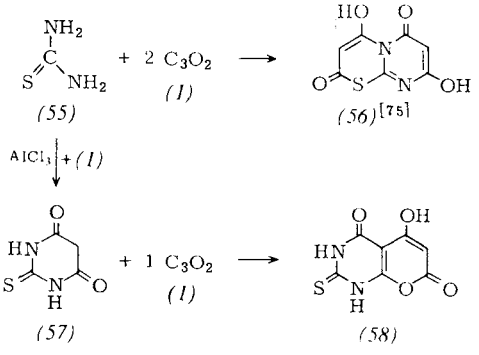


(52) *(53)*[81] *(54)*[81]

R = Phenyl[43], subst. Phenyl[65], 1-, 2-Naphthyl[43], 2-, 3-, 4-Pyridyl[43, 65]

+ *(1)* → etc.

According to *Dashkevich*[61, 83], thiourea *(55)* and *N*-arylthioureas afford thiobarbituric acid *(57)* and its *N*-aryl derivatives in the presence of $AlCl_3$. However, *Ziegler*[43] found that in the absence of $AlCl_3$ thiourea readily adds two moles of C_3O_2. It could recently be demonstrated that the sulfur is incorporated into the bicyclic ring system to form the pyrimidothiazine *(56)*[82]. In contrast, the thioxo group remains intact on reaction of thiobarbituric acid *(57)* with C_3O_2 to give the pyranopyrimidine *(58)*[82]. Hence it follows that



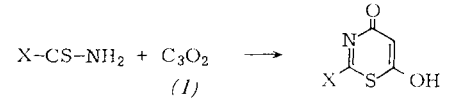
(55) *(56)*[75]

(57) *(58)*

(57) cannot be an intermediate in the formation of *(56)*. Instead, thiourea reacts with C_3O_2 as a "thioamide" to form a reactive 2-aminothiazinone which, as an "amidine", immediately reacts with a second molecule of *(1)* to give *(56)* (see Section 4.3.1).

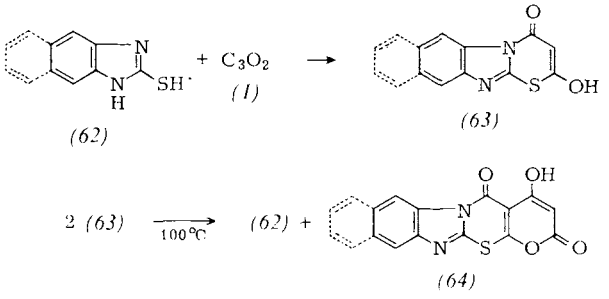
N-Acylthioureas *(59a)* afford 2-acylamino-6-hydroxy-1,3-thiazin-4-ones *(60)*[83] whereas dithiocarbamic esters *(59b)* react with *(1)* in acetonitrile or ethyl acetate to form the corresponding 2-alkylthio derivatives *(61)*[84].

Benzimidazole-2-thiol *(62)* exhibits a remarkable behavior in that it undergoes cycloaddition with C_3O_2 to form a thermolabile 1:1 adduct *(63)*. If this compound is heated for a

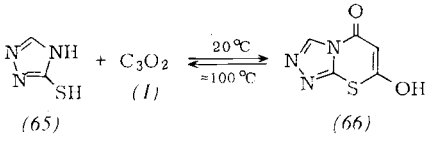


(59a), X = R-CO-NH *(60)*, X = R-CO-NH
(59b), X = R-S *(61)*, X = R-S

few minutes in five times the amount of pyridine, it decomposes to benzimidazole-2-thiol *(62)* and the pyrone derivative *(64)*[74]. Naphthimidazole-2-thiol behaves similarly[74].

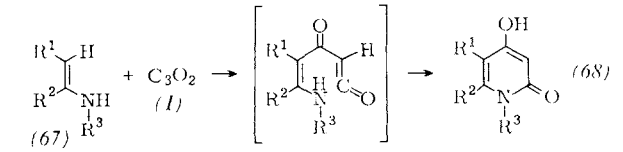


The addition product *(66)* formed from 1,2,4-triazole-3-thiol *(65)* and C_3O_2 is even more labile and decomposes to the starting materials on heating[74] [cf. the retrocleavage of mesomeric thiazine betaines *(121)*—*(123)*].



4.3.3. Heterocycles Containing One N Atom

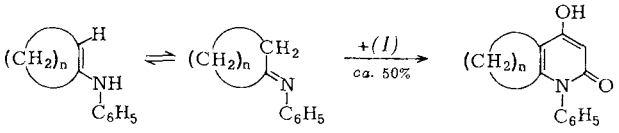
Enamine derivatives *(67)*, which are accessible from β-oxo esters or β-diketones by treatment with ammonia or primary aliphatic or aromatic amines, undergo ready reaction with C_3O_2 at 20 °C to form 4-hydroxy-2-pyridones *(68)*[85].



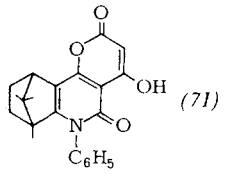
R^1 = $CO_2C_2H_5$, CO-CH_3; R^2 = Alk, Ar; R^3 = H, Alk, Ar

Reaction of the anils *(69a)*—*(69d)* with C_3O_2 *(1)* in ether to give the bicyclic 4-hydroxy-2-pyridones *(70a)*—*(70d)* proceeds somewhat less easily[86]. The anil of camphor proves to be an exception: it reacts with *(1)* only under drastic conditions (100 °C, 4 h) to give a poor yield of the pyranopyridinedione *(71)*[86].

In analogous manner, the hydrazones *(72)* can be converted into *N*-amino-4-hydroxy-2-pyridones in ether at 40—80 °C in an autoclave; the (readily separable) pyrone derivatives *(74)* are invariably formed as side products[87].

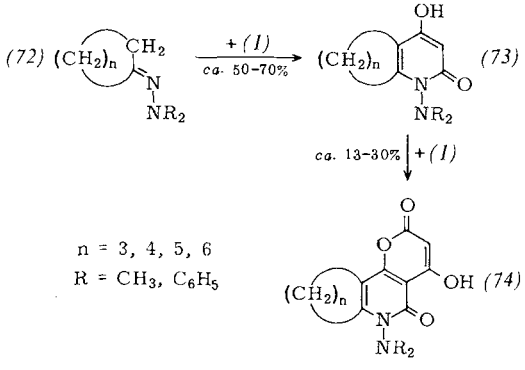


(69a)-*(69d)*, n = 3, 4, 5, 6 *(70a)*-*(70d)*

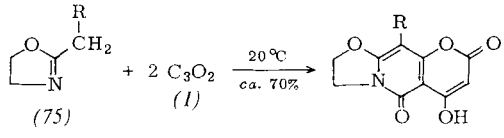


(71)

Another class of compounds containing an active methyl or methylene group α to a C=N double bond is found in the imidic esters. Cyclic imidic esters such as the 2-oxazolines

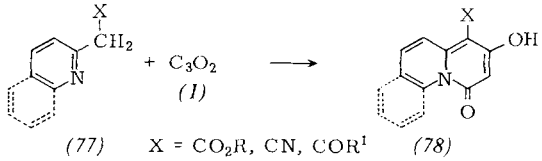


(75) afford only addition products with 2 mol of C_3O_2 even when the reaction is carried out in ether at 20 °C[88].



(a), R = H; *(b)*, R = CH_3 *(76)*

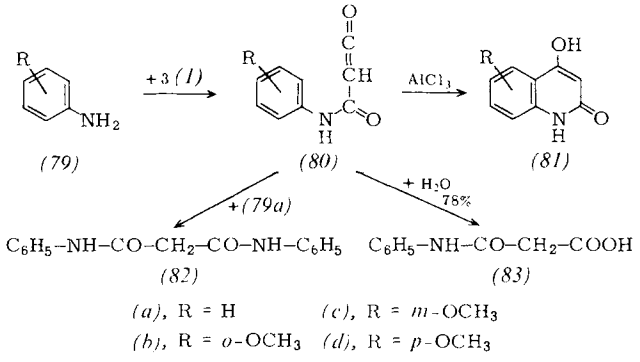
α-Picoline does not react with C_3O_2. However, if the side chain is activated by an ester[29], nitrile[29], or acyl group[89], then *(77)* gives almost quantitative yields of the 2-hydroxy-4-quinolizinones *(78)*. In the same manner, 2-quinolylacetic ester also yields the corresponding benzo derivative[90].



(77) X = CO_2R, CN, COR^1 *(78)*

The reaction of C_3O_2 with an excess of aniline affords malondianilide *(82)* quantitatively. This is frequently utilized in the quantitative determination[6e] of the C_3O_2 content of solutions in a method already employed by *Diels*[39]. However, *Omori*[91] has recently shown that, in the presence of $AlCl_3$ in refluxing benzene, reaction of C_3O_2 and aniline in a molar ratio of 3:1 yields 17% of 4-hydroxyquinolone *(81a)* alongside *(82)*. The transient occurrence of ketenecarboxanilide *(80)* can be demonstrated by formation of malonmonoanilide

(83) (78%) on addition of water to the reaction mixture (prior to heating in benzene). Higher yields (up to 67%) of

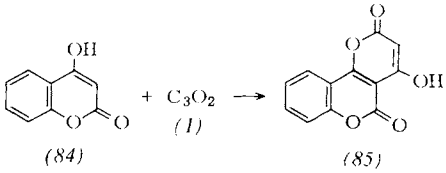


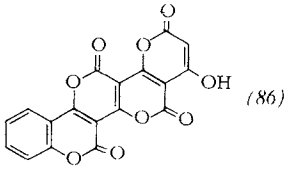
substituted quinolones (81b)—(81d) are obtained on use of methoxyanilines (79b)—(79d). Malondianilide (82) is known to afford 4-hydroxyquinolone (81a) in 93% yield on heating to 245—250 °C in the presence of $AlCl_3$[92]; not even traces of this compound are formed from (82) and $AlCl_3$ in refluxing benzene (80 °C)[93].

4.3.4. Heterocycles Containing One O Atom

Ring closure reactions of C_3O_2 to yield heterocycles containing one O atom as side or subsequent reactions have repeatedly been mentioned in the foregoing Sections; examples included formation of the pyrone derivatives (54), (58), (64), (71), (74), and (76). This property of C_3O_2 to react with heterocycles containing the malonyl grouping and with other electron-rich phenols in a process involving annelation of a 4-hydroxy-2-pyrone system was discovered by *Ziegler*[94] as long ago as 1961. Since 4-hydroxy-2-pyrones again contain a reactive malonyl grouping and can be regarded as an electron-rich phenolic system, this reaction can be induced to yield polypyrone derivatives if conducted in the presence of excess C_3O_2. The structural relationship of this class of compounds to "red coal" is discussed in Section 4.6. In the following we shall consider the reaction of carbon suboxide with phenolic compounds, ketones, and 1,3-diketones.

4-Hydroxycoumarin (84), which is itself a "malonic acid derivative" formed in high yield by self-cyclization of diphenyl malonate (87) at 150 °C in the presence of $AlCl_3$[95], adds one mole of C_3O_2 at 90 °C in THF to give the pyrone derivative (85) (*ca.* 50% yield). The reaction also yields polypyrones such as (86) which formally arises by addition of 4 mol of C_3O_2 to phenol, and which can also be synthesized in stepwise manner *via* reactive malonic esters[94, 96].

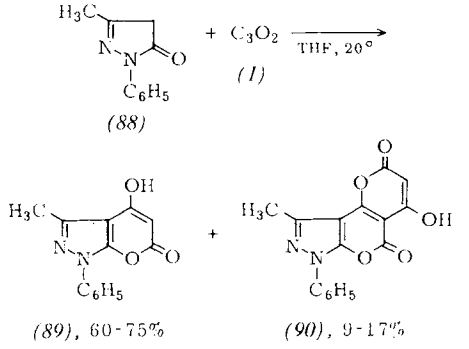




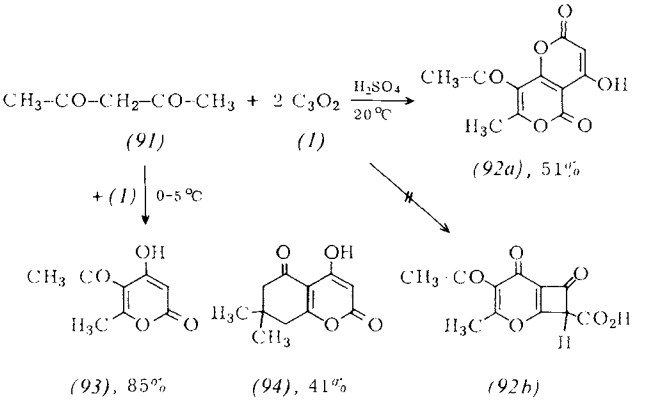
Direct reaction of C_3O_2 with phenol in the presence of $AlCl_3$[97] (*e.g.* in tetrachloroethane) affords 28% of diphenyl malonate (87) as major product, alongside very small amounts of compounds (84) and (85). On use of *o*-, *m*-, and *p*-cresol the yield of 4-hydroxycoumarins rises to *ca.* 10% while that of the pyrone derivatives remains constant at 0.5 to 1.1%. In the presence of H_2SO_4 however, only malonic esters are formed[97].

$$C_6H_5OH + C_3O_2 \xrightarrow[25\,^\circ C]{AlCl_3} 28\%\,CH_2(CO_2C_6H_5)_2 + 0.2\%\,(84) + 0.9\%\quad (85)$$
(1) (87)

Ring closure with (1) to give heterocycles containing one O atom also takes place with methyl(phenyl)pyrazolone (88). Depending upon the reaction conditions, the pyranopyrazolone (89) is accompanied by varying amounts of pyranopyranopyrazoledione (90)[43].



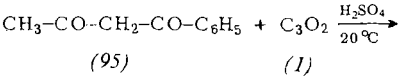
The action of C_3O_2 on β-diketones and β-oxo esters in the presence of H_2SO_4 was first described by *Hegar*[37]. This author showed that, *e.g.*, pentanedione (91) reacts with 2 mol of C_3O_2 in ether, and formulated the product as the cyclobutapyran derivative (92b). However, *Hradetzky* and *Ziegler*[98] were able to demonstrate that the product is actually the isomeric pyranopyrandione (92a) and that the reaction with $2C_3O_2$ can be applied to a series of further β-diketones. *Omori*[99] subsequently found that the 1:1 adduct (93) is also accessible in good yield on reaction of (91) with (1) in equimolar amounts below 5 °C; under analogous conditions he obtained the tetrahydrocoumarin derivative (94) from dimedone[97].



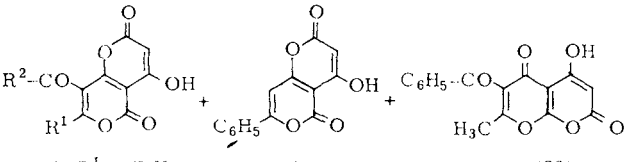
A much more complicated course is taken by the reaction of C_3O_2 with unsymmetrical β-diketones like benzoylacetone (95). A 2:1 addition would be predicted to yield the isomeric pyranopyrandiones (96a) and (96b) owing to the ambifunc-

tional character of *(95)*. In fact, *Omori*[99] isolated two products on reaction of *(95)* with C_3O_2, which he formulated as *(96a)* and *(96b)*, probably being ignorant of an earlier study[100]. According to *Ziegler et al.*[100], however, the major product of prolonged reaction (8 days) between *(1)* and *(95)* in ether and in the presence of H_2SO_4 is the "α,γ-pyronopyrone" *(98)* and the deacylated[101] "α,α-pyronopyrone" *(97)*[102]. Owing to the similarity in the melting points[100,102] and the spectroscopic data[102c], there is good reason for assuming that the substance formulated as *(96a)* by *Omori*[99] is in fact *(97)*[103].

This apparently somewhat obscure behavior of benzoylacetone *(95)* can be explained, not only by the fact that reaction of *(95)* with, *e.g.*, malonyl chloride leads initially to the two isomeric 4-hydroxy-2-pyrones *(99)* and *(100)* (which are undoubtedly intermediates in the reaction with C_3O_2) but above all by the rearrangement of *(100)* to *(99)* at the melting point (168 °C) or on acid catalysis[104]. Hence it is also understandable why the stable substance *(99)* gives exclusively *(98)* in good yield on treatment with C_3O_2 in the presence of H_2SO_4

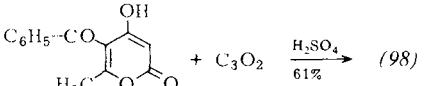


(95) *(1)*

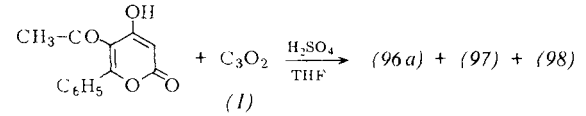


(96a), $R^1 = C_6H_5$, $R^2 = CH_3$
(96b), $R^1 = CH_3$, $R^2 = C_6H_5$

(97) *(98)*



(99) *(1)* *(98)*

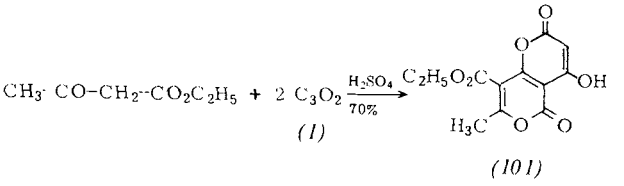


(100) *(1)* *(96a)* + *(97)* + *(98)*

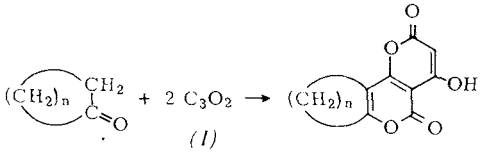
whereas the rearrangeable compound *(100)* furnishes a mixture of *(96a)*, *(97)*, and *(98)* which can only be separated by chromatography[100].

While acetoacetic ester and *(1)* give a 70% yield of the pyranopyrandione *(101)*[99], simple ketones lacking an additional activated methylene group are converted only with difficulty and in unsatisfactory yields into pyranopyrandiones. Thus cyclohexanone *(102a)* and cycloheptanone *(102b)* merely give 10—15% of the pyranopyrandiones *(103a)* and *(103b)* respectively after six to eight weeks' reaction (without H_2SO_4 as catalyst)[43]. Reaction of acetone with C_3O_2 (in ether with H_2SO_4) furnishes only 8% of the pyranopyrandione *(104)*[99]; a somewhat higher yield of *(104)* can be obtained from triacetolactone *(105)* and C_3O_2[98].

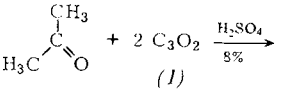
It appears remarkable that 1,3-dicarbonyl compounds react with C_3O_2 only in the presence of protic acids. Three explanations have so far been proposed for the catalytic action of H_2SO_4: formation of an electrophilic cation ($O{=}C{=}CH{-}\overset{\oplus}{C}{=}O$) by protonation of C_3O_2[99]; generation of reactive sulfuric malonic anhydrides[98]; and finally rupture of the hydrogen bonds in the enolized dicarbonyl compounds by the mineral acid[98].



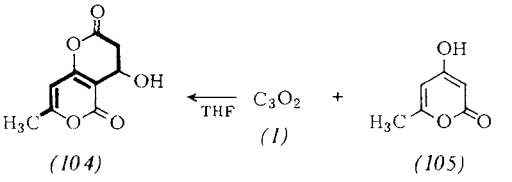
(1) *(101)*



(102a), *(102b)* *(1)* *(103a)*, *(103b)*
n = 4,5



(1)



(104) *(1)* *(105)*

All pyranopyrandiones react with ferric salts to give intensely colored 3:1 complexes which can be extracted from aqueous media by chloroform[93].

Particular mention should be made of the following fact: All pyranopyrandiones of the kind considered in this Section are "protected" polyoxocarboxylic acids. The significance of this class of compounds—especially the polypyrones such as compounds of type *(86)*—for the biosynthesis of phenolic natural products is known[105]. The protected β-trioxocarboxylic acid chain is shown in bold print in formula *(104)*. Action of alkalis on this compound under various conditions yields orsellinic acid, orcine, and other phenolic compounds which can themselves act as intermediates for natural products[96,105]. Other synthetic pathways have hitherto been commonly employed for the preparation of such polypyrone compounds. The above results would suggest that C_3O_2 may also be used to advantage for the production of such polypyrones (= polymalonyl compounds) (cf. also Section 4.6).

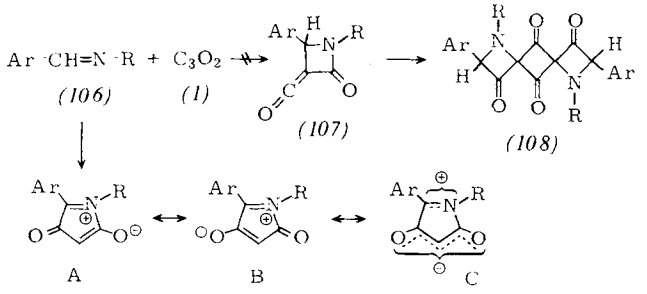
4.3.5. Reactions Leading to Mesoionic Heterocycles

4.3.5.1. Five-Membered Systems

It has been shown in Section 4.3.3 that azomethines with α-methyl or α-methylene groups afford 4-hydroxy-2-pyridones. In the absence of the acylatable group, as in the azomethines *(106)* derived from benzaldehydes, a completely novel reaction takes place with C_3O_2.

The reaction of benzylideneaniline with *(1)* was first reported by *Dashkevich*[106], who assigned the spiro structure *(108)* to the product and assumed a primary [2+2] addition to the β-lactam ketene *(107)* followed by [2+2] dimerization (cf. Section 4.4). In fact, however, the reaction does not afford

a 2:2 adduct but (as can be shown by mass spectrometry) instead a 1:1 adduct. *Sterk et al.*[107] proposed a zwitterionic structure *(109)* describable only in terms of a series of



(106) *(1)* *(107)* *(108)*

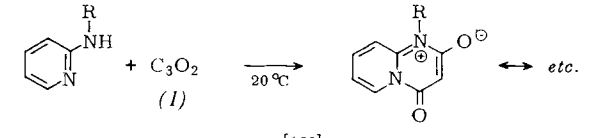
A B C

(109) Ar = C_6H_5; R = C_6H_5; *o*-, *m*-, *p*-C_6H_4Cl; *p*-C_6H_4Br; *p*-$C_6H_4NO_2$; *p*-$C_6H_4CH_3$; CH_3; C_2H_5; i-C_4H_9; C_6H_{11}; $CH_2C_6H_5$

resonance formulas (*e.g.* A↔B). The charge distribution in compounds *(109)* is probably best described by formulation C. Besides benzylideneaniline, a large number of other Schiff bases react similarly with C_3O_2[107,108]. In the preparation of compounds such as *(109)*, carbon suboxide can be successfully replaced by malonyl chloride[107].

4.3.5.2. Six-Membered Systems

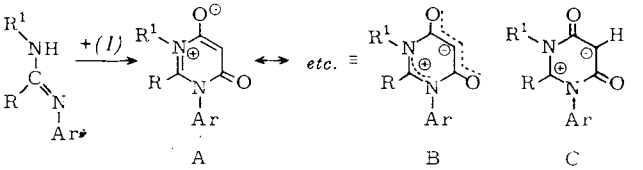
Amidines and monosubstituted amidines react with C_3O_2 to form hydroxypyrimidones (see Section 4.3.1) which exist predominantly in the tautomeric zwitterionic form[69]. *N,N'*-Disubstituted amidines such as *(110)* and *(112)* which contain only one replaceable H atom should accordingly yield "fixed" zwitterionic pyrimidines directly on reaction with *(1)*. That this does in fact occur was demonstrated simultaneously by *Potts*[109] and *Kappe*[110] in 1971 for *N*-substituted 2-aminopyridines *(110)* which afford the betaines *(111)* on reaction in ether.



(110) *(a)*, R = CH_3[109] *(b)*, R = C_6H_5[110] *(111)*

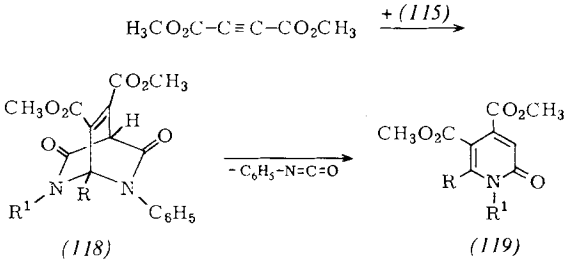
This reaction can also be applied to simple *N,N'*-disubstituted amidines *(112)* (including formamidines, R = H)[112]. In similar fashion, *N*-substituted amide oxime ethers *(113)* can yield *N*-alkoxypyrimidine betaines *(116)*[113]. Finally, further extension of this synthetic principle to *N,N'*-disubstituted *S*-alkylisothioureas *(114)* affords the 2-alkylthiopyrimidine zwitterions *(117)*[114].

Derivatives, *e.g.* of *(115)*, substituted at C-5 can also be prepared from reactive malonic esters and malonyl chlorides[110]; however, satisfactory results are obtained only with carbon suboxide for compounds that bear no substituents in the malonyl moiety. The resulting pyrimidine betaines *(111)* and *(115)*—*(117)* can also be described only by a series of canonical resonance formulas[110]. Formula B best describes the charge distribution, while the "sextet canonical structure" C indicates that these compounds are potential starting materials for 1,4-dipolar cycloadditions. Indeed, compounds *(111)* and *(115)* react very smoothly with reactive acetylenes, *e.g.* *(115)* with dimethyl acetylenedicarboxylate to form the addition compound *(118)*, which is, however, extremely prone to stabilization by loss of phenyl isocyanate, yielding 2-pyridones *(119)*[109,111,112]. This concept of preparing mesoionic heterocycles with the malonyl grouping can be applied to *N*-substituted thioamides (cf. Section 4.3.2); thus thiobenzamides *(120)* react with C_3O_2 in ether to give the mesomeric thiazine betaines *(121)*[115]. Similarly, pyridine- and pyrimi-



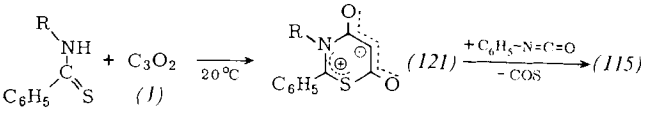
A B C

(112), R = H, C_6H_5; R^1 = C_6H_5, CH_3; Ar = C_6H_5[112] *(115)*
(113), R = C_6H_5; R^1 = $OCH_2C_6H_5$; Ar = C_6H_5[113] *(116)*
(114), R = SCH_3, SC_2H_5; R^1 = Ar = *o,p*-$C_6H_4CH_3$[114] *(117)*

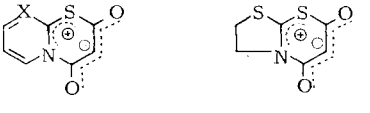


(118) *(119)*

dine-2-thiol furnish the zwitterionic 1,3-thiazines *(122a)* and *(122b)*, respectively, and 2-thiazoline-2-thiol the zwitterion *(123)*[115]. Thiazine betaines also undergo 1,4 dipolar cycload-



(120) *(a)*, R = C_6H_5 *(b)*, R = $CH_2C_6H_5$ *(121)*



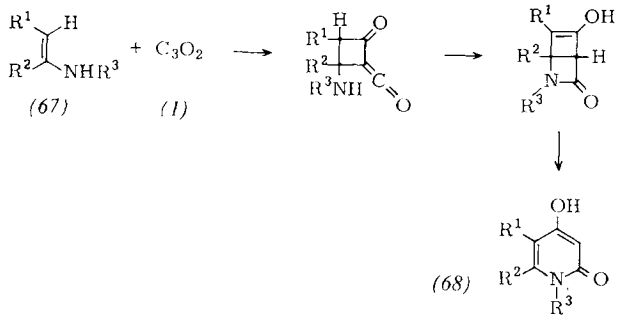
(122a), X = CH *(123)*
(122b), X = N

ditions; for instance, reaction with aryl isocyanates proceeds *via* an intermediate analogous to compound *(118)* with elimination of carbon oxide sulfide to give mesoionic pyrimidines, *e.g.* *(121)*→*(115)*[116]. When heated to above their melting point the thiazine betaines *(121)*—*(123)* eliminate C_3O_2. These substance can therefore be used as sources of carbon suboxide[115].

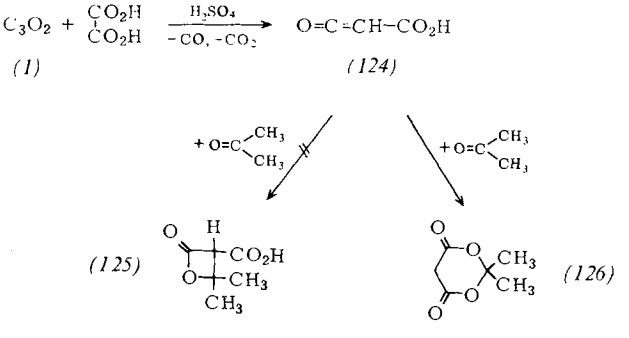
4.4. "Cycloadditions"

As already mentioned, C_3O_2 appears to behave as a "double ketene", and thus as a double electrophile, in all its reactions; hence any substrate is doubly acylated stepwise *via* a ketenecarboxylic derivative to form open-chain or cyclic malonic acid derivatives.

However, the question has repeatedly been raised whether C_3O_2 might not also undergo electrocyclic [2+2]-cycloadditions (*e.g.* $_\pi2_s+_\pi2_a$). For instance, *Ulrich*[6f] formulated the reaction of *(1)* with enamines such as *(67)* and *(69)* as proceeding *via* a bicyclic intermediate by analogy with the behavior of simple ketenes, albeit without experimental evidence.

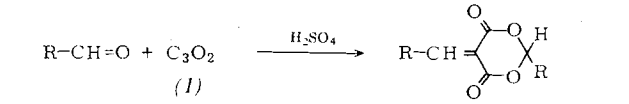


Assumption of a double [2+2] cycloaddition led *Dashkevich*[106] to (erroneously) assign the structure *(108)* to the reaction product obtained from *(1)* and benzylideneaniline. As early as 1924, *Diels*[39] described the reaction of acetone with *(1)* in the presence of oxalic acid and H_2SO_4 as a [2+2]-cycloaddition of the transient ketenecarboxylic acid *(124)* (the water arises from decomposition of the oxalic acid) to the C=O bond of acetone with formation of the β-lactone *(125)*. This concept of the reaction course has hitherto been incorporated in nearly all reviews[6b, 6c, 6e]. However, the reaction product obtained by *Diels* has been shown[93] to be Meldrum's acid *(126)*[117] and not *(125)*. Remarkably, the ester of the substituted ketenecarboxylic acid can indeed



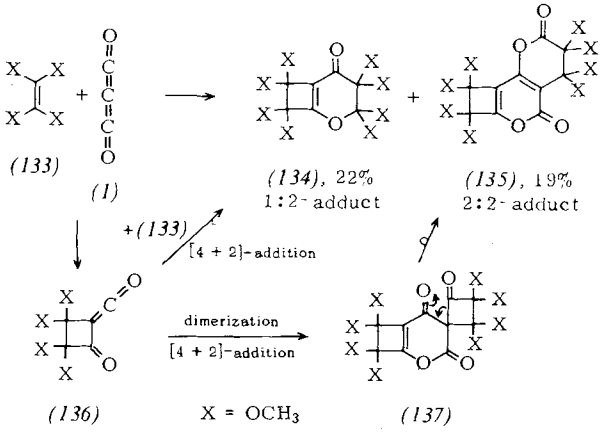
act as a $_\pi2_a$ component in [2+2]-cycloadditions, as *Sterk* recently demonstrated in the case of their dimerization[118]. Furthermore, the addition of ethyl ethylketenecarboxylate to benzylideneaniline yields a β-lactam as [2+2]-adduct; however, the reaction involves an isolable zwitterionic intermediate[119].

Reaction of the benzaldehydes *(127a)*—*(127c)* with *(1)* in ether and in the presence of H_2SO_4 likewise circumvents [2+2]-addition. According to *Hopf* and *Hegar*[120], the products are compounds *(130a)*—*(130c)* having a Meldrum's acid skeleton and not the β-lactones which are usually obtained from ketenes. Cinnamaldehyde *(128)* and thiophene-2-carbaldehyde *(129)* react in an analogous manner. The structure of the products is indicated unequivocally by degradation experiments. Moreover, *Wessely*[121] prepared *(130a)* independently and almost simultaneously by condensation of "phenyl-Meldrum's acid" with benzaldehyde. This synthesis also throws some light on the probable formation of *(130)*—*(132)*: A certain amount of water is inevitably introduced into the reaction system by the sulfuric acid; the resulting malonic acid (or malonic sulfuric anhydride) reacts with the aldehydes affording Meldrum's acids which undergo ready condensation with aldehydes to form unsaturated derivatives[117c] (the water functioning as catalyst being released in the process).



127) (a), R = C_6H_5, *(b)*, R = p-$C_6H_4CH_3$, *(c)*, R = p-C_6H_4Cl *(130)*
128) R = C_6H_5-CH=CH *(131)*
129) R = 2-Thienyl *(132)*

A detectable primary [2+2]-addition of C_3O_2 seems to have been reported only recently by *R. W. Hoffmann*[122] for an electron-rich olefin. After reaction of C_3O_2 with tetramethoxyethylene *(133)* in ether, approximately equal yields of a 1:2 adduct *(134)* and a 2:2 adduct *(135)* can be isolated. Since the structure of these compounds appears to be established, we are compelled to make the following mechanistic assumptions: The primary step is indeed a [2+2]-addition to yield the acylketene *(136)*. This reacts as a typical acylketene[123], either by [4+2]-addition with another molecule of tetramethoxyethylene *(133)* yielding the 1:2 adduct *(134)* or by dimerization to *(137)* which undergoes stabilization by a known type of rearrangement[124] to the pyranopyrandione *(135)*.

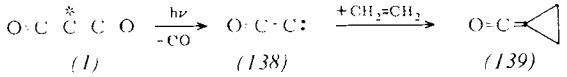


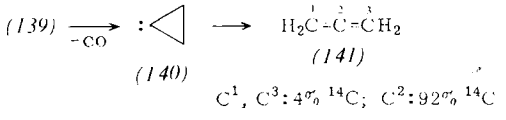
Summarizing, even though the available experimental evidence is still very sparse, the known reactions of *(1)* permit formulation of the following rule: In principle, carbon suboxide avoids the usual ketene addition reactions as long as the substrate contains two (or even only one, see Section 4.3.5) H atoms susceptible to electrophilic displacement.

4.5. Photochemical Reactions

Carbon suboxide undergoes a simple photochemical reaction with olefins[125–129]; a single carbon atom is inserted into the C=C double bond to form allenes and two molecules of CO. Thus ethylene furnishes allene *(141)* as major product alongside a little methylacetylene. By labeling the central C atom of C_3O_2 with ^{14}C it can be shown that this atom mainly provides the central C atom of the allene[126]. This reaction therefore bears a close formal resemblance to the

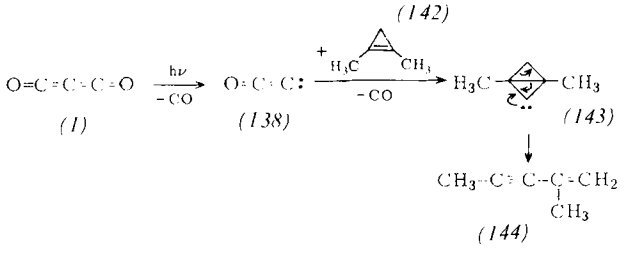
attack of carbon atoms on olefins[127a]. However, decomposition of C_3O_2 into 2 CO and $C(^3P)$ requires 141.5 kcal/mol, whereas the above photochemical reaction occurs already with 3000-Å light (corresponding to 95.3 kcal/einstein)[127b]. The initial photochemical step has therefore always been assumed to be decomposition of C_3O_2 into CO and carbonylcarbene *(138)*[125], which reacts with ethylene (and other alkenes) to give the high-energy ketene *(139)*. Subsequent elimination of another molecule of CO furnishes cyclopropylidene *(140)* which undergoes cyclopropylidene-allene rearrangement in the usual manner[127c].



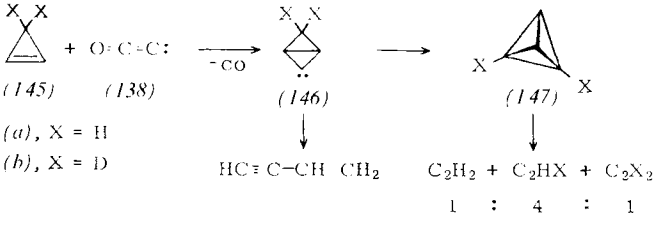


Studies by *Williamson* and *Bayes*[128] suggest the existence of *(138)* as a triplet and a singlet species. Photolysis of *(1)* at 3000 Å is reported to give C_2O ($X^3\Sigma$), while C_2O ($\tilde{a}\ ^1\Delta$) is generated at 2500 Å. Whereas the singlet carbene reacts fairly unselectively, the triplet species clearly displays electrophilic properties (in contrast to the views held by other authors[129]). This observation accords with the fact that *(138)* reacts faster with ethylene homologs (*e.g.* 40× faster with isobutylene) than with ethylene itself[125, 128].

The reactions with cyclopropene derivatives are also interesting since cyclopropylidene-allene rearrangement would then lead to a highly strained structure. Thus, according to *A. P. Wolf*[130], 1,2-dimethylcyclopropene *(142)* undergoes an alternative reaction *via* the carbene *(143)* to yield 2-methyl-1-penten-3-yne *(144)* as major product. No evidence could be found for the intermediacy of a tetrahedrane in this reaction.



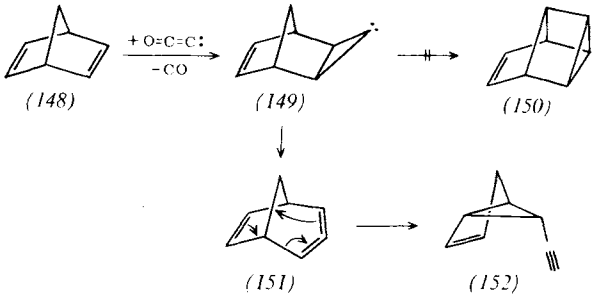
In a later study, however, the same research group[131] were unable to rationalize a reaction of cyclopropene *(145a)* and its 3,3-dideuterated derivative *(145b)* except by assuming a tetrahedrane intermediate. In accord with the above mechanism, cyclopropene and C_3O_2 give a 33% yield of vinylacetylene *via* the bicyclic carbene *(146)*. 24% of acetylene



is also formed (yields based on reacted cyclopropene). 3,3-Dideuteriocyclopropene *(145b)* affords acetylene, monodeuterioacetylene, and dideuterioacetylene in the ratio 1:4:1. This result rules out all plausible mechanisms for acetylene formation except that proceeding *via* the tetrahedrane *(147)*.

Klumpp and *Van Dijk*[132] attempted to synthesize the unknown compound tetracyclo[3.3.0.$0^{2,4}$.$0^{3,6}$]oct-7-ene *(150)* from norbornadiene *(148)* *via* the carbene *(149)* by a C—H insertion reaction. However, photolysis of C_3O_2 in the presence of *(148)* affords only a C_8H_8 compound which is isomeric with *(150)*, namely the alkyne *(152)*. The reaction can proceed *via* the strained allene *(151)* as intermediate[133]; however, other routes are also conceivable[132, 134].

Interestingly, it follows from the above observations that in photochemical reactions C_3O_2 undergoes successive loss of two CO molecules, showing a close resemblance to the reactions of atomic carbon[127d]. Photolysis has so far been studied



in detail only for olefins. It may be expected that the possible applications of :CCO in preparative organic chemistry are much greater.

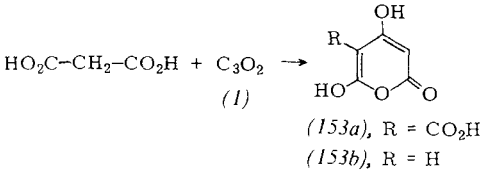
4.6. Polymerization

Since its discovery[1], the polymerization of carbon suboxide has been studied by numerous chemists. Results prior to 1968 are surveyed in "Gmelins Handbuch"[5]. Reference should be made here to a widespread fallacy concerning the ease of polymerization[6a-6c, 6e] of C_3O_2. As early as 1922, *Ott* and *Schmidt*[13] demonstrated that carefully purified C_3O_2 can be kept unchanged for long periods, and this observation has repeatedly been confirmed[5, 48, 94, 135]. Even then, our experience has shown that polymerization only occurs when traces of water or other proton-releasing (or nucleophilic) substances are present. "High-temperature polymerization", as well as polymerizations[5] induced by radiolysis or photolysis, appear to be exceptions.

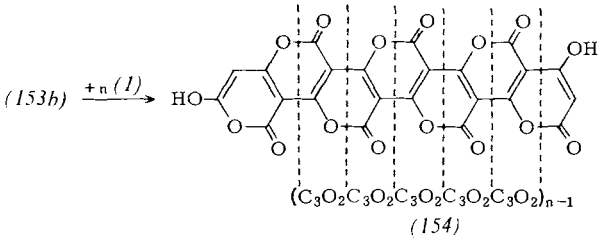
The intensely colored polymers are usually termed "red carbon" in the earlier literature; this rather inaccurate designation was later[136] changed to "red coal". The similarity between "polymeric C_3O_2" and C_3O_2 addition products with a variety of substrates (*e.g.* phenolic compounds) prompted *Ziegler*[19, 137] in 1960 to postulate a close constitutional relationship between polypyrone compounds—*e.g.* *(86)*—and "red coal". Supporting evidence for these views on the structure of poly-α-pyrones has been gathered by other authors[138-140] from spectroscopic and X-ray studies.

Water-induced[141] polymerization has already been formulated as proceeding *via* an acetonedicarboxylic anhydride intermediate *(153b)*[94], whose formation is simply explained by

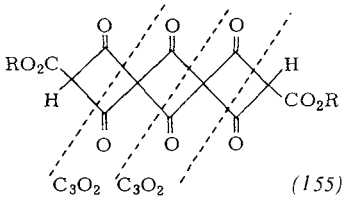
addition of *(1)* to malonic acid and decarboxylation of the primary product *(153a)*. This concept received support from IR and UV studies on the induction phase[5] of the "polymerization" of C_3O_2 to "red coal"[135]. In this way it also proved possible to discount structural investigations[142] on "red coal", in which UV spectra were interpreted in a manner supporting the former Diels formulation[6a, 39] as polyspirocyclobutanedione *(155)*.



(153a), R = CO_2H
(153b), R = H



(154)



(155)

The use of C_3O_2 to produce graft polymers represents a recent application. *Bukowski* and *Porejko* have copolymerized "polyamide 6" (polycaprolactam) in toluene with C_3O_2[143a] Grafting of C_3O_2 onto polyethylene films proved possible after initial activation of the polyethylene by UV or γ irradiation or by ozonization[143b]. Cross-linked products having novel properties are obtained in both cases.

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[1] *O. Diels* and *B. Wolf*, Ber. Deut. Chem. Ges. *39*, 689 (1906).

[2] Formulation as the lactone of hydroxypropiolic acid, as was first proposed by *A. Michael*, Ber. Deut. Chem. Ges. *41*, 925 (1908), was a subject of protracted controversy [6a—6e].

[3] Regarding the influence of this unexpected discovery of a new oxide of carbon on the further career of *Diels*, see the obituary by *S. Olsen*, Chem. Ber. *95*, V (1962).

[4] *O. Diels* and *G. Meyerheim*, Ber. Deut. Chem. Ges. *40*, 355 (1907).

[5] Gmelins Handbuch der Anorganischen Chemie. Kohlenstoff, C, Section 1, Syst. No. 14, pp. 75—99. Verlag Chemie, Weinheim 1970 (the literature is covered up to 1968).

[6] For earlier surveys, see: a) *O. Diels*, Z. Angew. Chem. *39*, 1025 (1926); b) *L. H. Reyerson* and *K. Kobe*, Chem. Rev. *7*, 479 (1930); c) *R. Grauer*, Chimia *14*, 11 (1960); d) *L. B. Dashkevich*, Russ. Chem. Rev. *36*, 391 (1967); e) *D. Borrmann* in Houben-Weyl-Müller: Methoden der Organischen Chemie. Thieme, Stuttgart 1968, Vol. 7/4, p. 286; f) *H. Ulrich*: Cycloaddition Reactions of Heterocumulenes. Academic Press, New York 1967, p. 100.

[7] For a critical and comparative review of the literature on this method, see ref. [8].

[8] *L. Crombie, P. A. Gilbert*, and *R. P. Houghton*, J. Chem. Soc. *C 1968*, 130.

[9] *L. B. Dashkevich*, Dokl. Akad. Nauk SSSR *132*, 1319 (1960); Engl. Transl. 707; *L. B. Dashkevich, V. A. Buevich*, and *B. E. Kubaev*, Zh. Obshch. Khim. *30*, 1946 (1960), Engl. Transl. 1925; cf. also *V. Maxia, S. Meloni, G. Parenti, M. A. Rolliera*, and *M. Secci*, Ric. Sci. Rend. *2 A*, 273 (1962).

[10] *H. Staudinger* and *S. Bereza*, Ber. Deut. Chem. Ges. *41*, 4461 (1908).

[11] *H. Hopf* and *G. Hegar*, Helv. Chim. Acta *44*, 2016 (1961).

[12] *E. T. Blues, D. Bryce-Smith, H. Hirsch*, and *M. J. Simons*, Chem. Commun. *1970*, 699.

[13] *E. Ott*, Ber. Deut. Chem. Ges. *47*, 2388 (1914); *E. Ott* and *K. Schmidt*, *ibid. 55*, 2126 (1922).

[14] A discussion of all mechanistic possibilities of formation of *(1)* from *(7)* which also explain the occurrence of acetic acid and CO will be found in ref. [8].

[15] Earlier results are given in ref. [5]. A critical treatment of more recent literature is to be found in refs. [16, 17].

[16] *T. R. Dyke, W. Klemperer, A. P. Ginsberg*, and *W. E. Falconer*, J. Chem. Phys. *56*, 3993 (1972).

[17] *J. R. Sabin* and *H. Kim*, J. Chem. Phys. *56*, 2195 (1972).

[18] *H. D. Rix*, J. Chem. Phys. *22*, 429 (1954).

[19] *F. A. Miller* and *W. G. Fately*, Spectrochim. Acta *20*, 253 (1964); and further references cited therein.

[20] *F. A. Miller, D. H. Lemmon*, and *R. E. Witnowski*, Spectrochim. Acta *21*, 1709 (1965).

[21] *W. H. Smith* and *G. E. Leroi*, J. Chem. Phys. *45*, 1767 (1966).

[22] *W. J. Lafferty, A. G. Maki*, and *E. K. Plyler*, J. Chem. Phys. *40*, 224 (1964).

[23] *W. H. Smith* and *J. J. Barrett*, J. Chem. Phys. *51*, 1475 (1969).

[24] *R. L. Livingstone* and *R. N. C. Rao*, J. Amer. Chem. Soc. *81*, 285 (1959); *A. Almenningen, S. P. Bastiansen, H. M. Seip*, and *R. Seip*, Chem. Phys. Lett. *1*, 569 (1968).

[25] For experimentally determined internuclear distances see ref. [5], p. 83.

[26] *U. Gelius, C. J. Allan, D. A. Allison, H. Siegbahn*, and *K. Siegbahn*, Chem. Phys. Lett. *11*, 224 (1971); *J. W. Rabalais, T. Bergmark, L. O. Werme, L. Karlson, M. Hussain*, and *K. Siegbahn*, Electron Spectrosc., Proc. Int. Conf. 1971 (Pub. 1972) 425—39; Chem. Abstr. *78*, 9987 v (1973).

[27] *J. F. Olsen* and *L. Burnelle*, J. Phys. Chem. *73*, 2298 (1969).

[28] *E. Ziegler*, Chimia *24*, 62 (1970); survey.

[29] *Th. Kappe*, Monatsh. Chem. *98*, 874 (1967).

[30] *G. Hagelloch* and *E. Fees*, Chem. Ber. *84*, 751 (1951).

[31] *L. B. Dashkevich* and *E. N. Kuvaeva*, Tr. Leningrad. Khim.-Farm. Inst. *16*, 59 (1962); Chem. Abstr. *61*, 2965c (1964); *L. B. Dashkevich* and *V. A. Pechenyuk*, Zh. Org. Khim. *3*, 636 (1967).

[32] *C. L. Wilson*, J. Chem. Soc. *1935*, 492; *A. F. Potter* and *H. L. Ritter*, J. Phys. Chem. *58*, 1040 (1954); cf. also *L. B. Dashkevich* and *V. M. Siraya*, Zh. Obshch. Khim. *32*, 2747 (1962); Engl. Transl. 2706.

[33] *L. B. Dashkevich* and *V. Beilin*, Zh. Obshch. Khim. *31*, 1671 (1961).

[34] *L. B. Dashkevich* and *E. N. Kuvaeva*, Zh. Obshch. Khim. *31*, 1669 (1961).

[35] *W. F. Ross* and *H. N. Christensen*, J. Biol. Chem. *137*, 89, 101 (1941); *W. F. Ross* and *L. S. Green*, *ibid. 137*, 105 (1941); *A. H. Tracy* and *W. F. Ross*, *ibid. 142*, 871 (1942); *146*, 63 (1942).

[36] *H. L. Fraenkel-Conrat*, J. Biol. Chem. *152*, 385 (1944).

[37] *G. Hegar*, Dissertation, ETH Zürich 1961.

[38] *L. B. Dashkevich* and *V. A. Pechenyuk*, Zh. Obshch. Khim. *35*, 253 (1965); Engl. transl. 256.

[39] *O. Diels, R. Beckmann*, and *G. Tönnies*, Liebigs Ann. Chem. *439*, 76, 92 (1924).

[40] *C. D. Hurd* and *F. D. Pilgrim*, J. Amer. Chem. Soc. *55*, 758 (1933).

[41] *H. Strangas*, Dissertation, Universität Graz 1973.

[42] *E. Ziegler, A. Argyrides*, and *W. Steiger*, Z. Naturforsch. *27b*, 1169 (1972).

[43] *E. Ziegler* and *H. Biemann*, Monatsh. Chem. *93*, 34 (1962).

[44] *L. B. Dashkevich* and *L. N. Kuzmenkow*, Zh. Obshch. Khim. *29*, 2367 (1959); Engl. transl. 2330.

[45] *L. B. Dashkevich* and *E. I. Boksiner*, Zh. Obshch. Khim. *28*, 2845 (1958); Chem. Abstr. *53*, 8065b (1959).

[46] *H. Staudinger*: Die Ketene. Enke, Stuttgart 1912.

[47] *H. Binder* and *W. Lindner*, J. Chromatogr. *77*, 323 (1973).

[48] *W. Lindner*, Dissertation, Universität Graz 1972.

[49] *E. Ziegler* and *H. Junek*, Monatsh. Chem. *86*, 506 (1955); *87*, 212, 218 (1956); cf. also *E. Ziegler*, Österr. Chem.-Ztg. *59*, 155 (1958), survey.

[50] *E. Ziegler* and *H. Sterk*, Monatsh. Chem. *98*, 1104 (1967).

[51] Concerning the detection of intermediate ketenecarboxylic acid derivatives by isotopic labeling, see *E. Ziegler, H. Sterk*, and *W. Steiger*, Monatsh. Chem. *101*, 762 (1970).

[52] *J. Billman, G. E. Tripp,* and *R. V. Cash,* J. Amer. Chem. Soc. *62,* 770 (1940); *L. B. Dashkevich* and *L. G. Izrailev,* Zh. Obshch. Khim. *30,* 3060 (1960); Engl. Transl. 3033.

[53] *L. B. Dashkevich,* Dissertation, Institute of Chemistry and Pharmacy, Leningrad 1966.

[54] *J. Billman* and *C. M. Smith,* J. Amer. Chem. Soc. *61,* 458 (1939); *74,* 3174 (1952).

[55] *D. J. Cram* and *R. L. Zimmermann,* J. Amer. Chem. Soc. *74,* 2646 (1952).

[56] The mechanisms leading to these side products are discussed in ref. [55].

[57] See ref. [6f], p. 40, and the literature cited in ref. [55]; compare, *e.g.*, the dimerization of the "masked" acetylketene diketene to dehydroacetic acid *(27b)*.

[58] *H. Wittman, V. Illi,* and *E. Ziegler,* Monatsh. Chem. *98,* 1108 (1967); *H. Wittman* and *H. Rathmayer,* Z. Naturforsch. *27b,* 528 (1972).

[59] *J. Van Alphen,* Rec. Trav. Chim. Pays-Bas *43,* 823 (1924).

[60] *J. M. Quintilla,* Span. Pat. 211.285 (1953); Chem. Abstr. *49,* 14812 (1955).

[61] *L. B. Dashkevich* and *V. M. Siraya,* Zh. Obshch. Khim. *32,* 2330 (1962); Chem. Abstr. *58,* 7946a (1963).

[62] *V. Segers,* Belg. Pat. 508.085 (1952); Chem. Abstr. *52,* 9218 (1958).

[63] See also earlier publications by: *A. E. Pauw,* Rec. Trav. Chim. Pays-Bas *55,* 215 (1936); *J. Th. L. B. Rameau, ibid.* 57, 199 (1938).

[64] *V. V. Korshak, S. V. Rogozhin,* and *V. I. Volkov,* Vysokomol. Soedin *1,* 799 (1959); Chem. Abstr. *54,* 17260e (1960); *S. Porejko et al.,* Polymery *9,* 58 (1964); Chem. Abstr. *61,* 9587e (1964).

[65] *E. Ziegler* and *R. Wolf,* Monatsh. Chem. *95,* 1061 (1964).

[66] *V. G. Beilin, L. B. Dashkevich,* and *S. P. Saenchuk,* Zh. Org. Khim. *6,* 1932 (1970); Chem. Abstr. *73,* 120587a (1970).

[67] *A. W. Dox* and *L. Yoder,* J. Amer. Chem. Soc. *44,* 361 (1921); *L. P. Ferris* and *A. R. Ronzio, ibid. 62,* 606 (1940).

[68] *M. Freund* and *K. Fleischer,* Liebigs Ann. Chem. *379,* 27 (1911).

[69] Regarding the tautomerism of class of substances, see *A. R. Katritzky, F. D. Popp,* and *A. J. Waring,* J. Chem. Soc. B *1966,* 565.

[70] *L. B. Dashkevich,* Zh. Obshch. Khim. *32,* 2346 (1962); Chem. Abstr. *58,* 7946c (1963).

[71] *E. Ziegler, A. Argyrides,* and *W. Steiger,* Monatsh. Chem. *102,* 301 (1971).

[72] *A. E. Tschitschibabin,* Ber. Deut. Chem. Ges. *57,* 1168 (1924).

[73] *E. S. Korbelainen,* "Mater. Nauch. Konf. LKhFI *1966,* 42.

[74] *E. Ziegler* and *R. Wolf,* Monatsh. Chem. *93,* 1441 (1962).

[75] In the following all condensed hydroxypyrimidones (*e.g. (44)–(51), (56)*) will be represented by only one tautomeric hydroxy form since no detailed studies are available on this point (especially concerning compounds with annelated five-membered rings). See: *A. R. Katritzky* and *J. M. Lagowski,* Advan. Heterocycl. Chem. *1,* 339 (1963); *A. R. Katritzky,* Chimia *24,* 134 (1970). Only in the case of *(43a)* a tautomeric ratio of 20:1 in favor of the betaine form has been determined: *A. R. Katritzky* and *A. J. Waring,* J. Chem. Soc. *1962,* 1544.

[76] *L. B. Dashkevich* and *E. S. Korbelainen,* Khim. geterotsikl. Soedin. *1965,* 597.

[77] *L. B. Dashkevich* and *E. S. Korbelainen,* Zh. Obshch. Khim. *34,* 3427 (1964); Engl. transl. 3470; Chem. Abstr. *62,* 4030b (1965).

[78] *L. B. Dashkevich,* Zh. Obshch. Khim. *31,* 3723 (1961); Engl. transl. 3477; Chem. Abstr. *57,* 8556a (1962).

[79] *L. B. Dashkevich,* Khim. geterotsikl. Soedin. *1966,* 602.

[80] For the preparation of this class with other malonic acid derivatives see: *J. Goerdeler* and *H. Horstmann,* Chem. Ber. *93,* 671 (1960); *E. Ziegler* and *E. Steiner,* Monatsh. Chem. *95,* 147 (1964).

[81] The formulations chosen here for *(53)* and *(54)* (tautomers and isomers respectively) deviate in some cases from the original literature and are based on more recent studies [82].

[82] *Th. Kappe, G. Lang,* and *E. Ziegler,* Z. Naturforsch. *29b,* 258 (1974).

[83] *N. A. Baranova, V. G. Beilin,* and *L. B. Dashkevich,* Zh. Org. Khim. *6,* 1734 (1970); Chem. Abstr. *73,* 109757k (1970).

[84] *V. G. Beilin, L. B. Dashkevich,* and *E. N. Kirillova,* Zh. Org. Khim. *6,* 2609 (1970); Chem. Abstr. *74,* 64232n (1971).

[85] *E. Ziegler* and *F. Hradetzky,* Monatsh. Chem. *95,* 1247 (1964).

[86] *E. Ziegler, F. Hradetzky,* and *M. Eder,* Monatsh. Chem. *97,* 1394 (1966).

[87] *E. Ziegler, E. Prewedourakis, H. Wittmann,* and *G. Kollenz,* Monatsh. Chem. *101,* 680 (1970).

[88] *Th. Kappe, M. A. Chirazi, H. P. Stelzel,* and *E. Ziegler,* Monatsh. Chem. *103,* 586 (1972). Oxazolidines react merely to give open-chain malondiamides: *L. B. Dashkevich* and *F. G. Sepel,* Khim. geterotsikl. Soedin. *1965,* 832.

[89] *Th. Kappe* and *Y. Linnau,* to be published.

[90] *Th. Kappe,* Monatsh. Chem. *98,* 2148 (1967).

[91] *A. Omori, N. Sonoda,* and *S. Tsutsumi,* Bull. Chem. Soc. Jap. *43,* 1135 (1970); Chem. Abstr. *73,* 14642e (1970).

[92] *E. Ziegler, R. Wolf,* and *Th. Kappe,* Monatsh. Chem. *96,* 418 (1965); concerning *(80)* as intermediate, see *E. Ziegler* and *H. Junek, ibid. 87,* 503 (1956).

[93] *Th. Kappe,* unpublished results.

[94] *E. Ziegler, H. Junek,* and *H. Biemann,* Monatsh. Chem. *92,* 927 (1961).

[95] *E. Ziegler* and *H. Junek,* Monatsh. Chem. *86,* 29 (1955).

[96] For the extension of this method and the application of the procedure to other substances such as *(104)* and *(105)*, see *T. Money et al.,* Tetrahedron *23,* 3435 (1967); cf. also ref. [105].

[97] *A. Omori, N. Sonoda, Y. Uchida,* and *S. Tsutsumi,* Bull. Chem. Soc. Jap. *42,* 3233 (1969).

[98] *F. Hradetzky* and *E. Ziegler,* Monatsh. Chem. *97,* 398 (1966).

[99] *A. Omori, N. Sonoda,* and *S. Tsutsumi,* J. Org. Chem. *34,* 2480 (1969).

[100] *E. Ziegler, M. Eder, F. Hradetzky,* and *E. Prewedourakis,* Monatsh. Chem. *98,* 2432 (1967).

[101] Removal of acyl groups from positions 3 or 5 of 4-hydroxy-2-pyrones by thermolysis [102a] or the action of H_2SO_4 is a known reaction: cf., *e.g.*, ref. [104] and literature cited therein.

[102] a) *E. Ziegler* and *H. Junek,* Monatsh. Chem. *89,* 323 (1958); b) *C. Goetschel* and *C. Mentzer,* Bull. Soc. Chim. Fr. *1962,* 356; c) *J. L. Douglas* and *T. Money,* Can. J. Chem. *45,* 1990 (1967).

[103] It cannot be decided unequivocally whether *(96b)* and *(98)* are identical; both research groups [99, 100] give practically the same melting point (226–228 and 229 C) but differing spectroscopic data. Rearrangement of one form into the other below the melting point is conceivable.

[104] *E. Ziegler* and *F. Hradetzky,* Monatsh. Chem. *97,* 710, 1046 (1966); *M. Eder, E. Ziegler,* and *E. Prewedourakis, ibid. 99,* 1395 (1968).

[105] *T. Money,* Chem. Rev. *70,* 553 (1970); and references cited therein.

[106] *L. B. Dashkevich* and *E. N. Kuvaeva,* Tr. Leningrad. Khim.-Farm. Inst. *16,* 55 (1962); Chem. Abstr. *61,* 2981c (1964).

[107] *H. Sterk, P. Tritthart,* and *E. Ziegler,* Monatsh. Chem. *102,* 1090 (1971).

[108] *E. Ziegler, W. Steiger,* and *H. Strangas,* to be published.

[109] *K. T. Potts* and *M. Sorm,* J. Org. Chem. *36,* 8 (1971).

[110] *Th. Kappe* and *W. Lube,* Monatsh. Chem. *102,* 781 (1971).

[111] *Th. Kappe* and *W. Lube,* Angew. Chem. *83,* 967 (1971); Angew. Chem. internat. Edit. *10,* 925 (1971).

[112] *K. T. Potts* and *M. Sorm,* J. Org. Chem. *37,* 1422 (1972).

[113] *E. Ziegler* and *A. Argyridis,* to be published.

[114] *E. Ziegler, H. Strangas,* and *W. Steiger,* to be published.

[115] *Th. Kappe* and *W. Golser,* Synthesis *1972,* 312.

[116] *Th. Kappe* and *W. Golser,* to be published.

[117] a) *A. N. Meldrum,* J. Chem. Soc. *93,* 601 (1908); b) regarding the structure, see *D. Davidson* and *S. A. Bernard,* J. Amer. Chem. Soc. *70,* 3426 (1948); c) for significance of the unsaturated derivatives as Lewis acids see *F. J. Kunz, P. Margaretha,* and *O. E. Polansky,* Chimia *24,* 165 (1970).

[118] *H. Sterk,* Z. Naturforsch. *27b,* 143 (1972); and further references cited therein.

[119] *W. Steiger, H. Sterk,* and *E. Ziegler,* Monatsh. Chem. *101,* 891 (1970).

[120] *H. Hopf* and *G. Hegar,* Helv. Chim. Acta *44,* 2016 (1961).

[121] *J. Swoboda, J. Derkosch,* and *F. Wessely,* Monatsh. Chem. *91,* 188 (1960).

[122] *J. Gelhaus, R. W. Hoffmann,* and *H. J. Lindner,* Chem. Ber. *104,* 861 (1971).

[123] *R. Gompper,* Angew. Chem. *81,* 348 (1969); Angew. Chem. internat. Edit. *8,* 312 (1969); *H. Stetter* and *K. Kiehs,* Chem. Ber. *98,* 1181, 2099 (1965); *G. Jäger, ibid. 105,* 137 (1972); and references cited therein.

[124] *P. Yates* and *E. A. Chandross,* Tetrahedron Lett. *1959,* (20) 1.

[125] a) *K. D. Bayes,* J. Amer. Chem. Soc. *83,* 3712 (1961); *84,* 4077 (1962); *85,* 1730 (1963); b) *C. Willis* and *K. D. Bayes, ibid. 88,* 3203 (1966).

[126] *R. T. Mullen* and *A. P. Wolf,* J. Amer. Chem. Soc. *84,* 3712 (1962).

[127] *W. Kirmse:* Carbene, Carbenoide und Carbenanaloga. Verlag Chemie, Weinheim 1969; a) pp. 157, b) 158, c) 156, d) 231.

[128] *D. G. Williamson* and *K. D. Bayes,* J. Amer. Chem. Soc. *90,* 1957 (1968).

[129] *R. T. K. Baker, J. A. Kerr,* and *A. F. Trotman-Dickenson,* J. Chem. Soc. *A 1966,* 975.

[130] *H. W. Chang, A. Lautzenheiser,* and *A. P. Wolf,* Tetrahedron Lett. *1966,* 6295.

[131] *P. B. Shevlin* and *A. P. Wolf,* J. Amer. Chem. Soc. *92,* 406 (1970).

[132] *G. W. Klumpp* and *P. M. Van Dijk*, Rec. Trav. Chim. Pays-Bas *90*, 381 (1971).

[133] For instance, 1,2-cyclohexadiene could be trapped as the simplest six-membered cyclic allene: *W. R. Moore* and *W. R. Moser*, J. Org. Chem. *35*, 908 (1970).

[134] *(149)* and *(152)* can be regarded, *e.g.*, as homovinylogs of *(143)* and *(144)*.

[135] *H. Sterk*, *P. Tritthart*, and *E. Ziegler*, Monatsh. Chem. *101*, 1851 (1970).

[136] *L. Schmidt*, *H. P. Boehm*, and *U. Hoffmann*, Z. Anorg. Allg. Chem. *282*, 241 (1955); 296, 246 (1958).

[137] *E. Ziegler*, Angew. Chem. *72*, 582 (1960).

[138] *R. N. Smith*, *D. A. Young*, *E. N. Smith*, and *C. C. Carter*, Inorg. Chem. *2*, 829 (1963).

[139] *A. R. Blake*, *W. T. Eeles*, and *P. P. Jennings*, Trans. Faraday Soc. *60*, 691 (1964); cf. also *A. O. Diallo*, J. Chim. Phys. *61*, 1409 (1964).

[140] *B. D. Kybett*, *G. K. Johnson*, *C. K. Barker*, and *J. L. Margrave*, J. Phys. Chem. *69*, 3603 (1965).

[141] Small amounts of acetic acid arising in the preparation can initiate polymerization in a similar manner, *e.g. via* malonic acetic anhydrides.

[142] *J. Wojtczak*, *L. Weimann*, and *J. M. Konarski*, Monatsh. Chem. *99*, 501 (1968).

[143] a) *A. Bukowski* and *S. Porejko*, J. Polym. Sci., Part A-1, *8*, 2491 (1970); b) *ibid.* *8*, 2501 (1970).

State of Development of Atomic Absorption Spectrometry[**]

New analytical methods (1)

By Hans Massmann[*]

Atomic absorption spectrometry has developed extremely rapidly in recent years, and is now used in many analytical laboratories. The purpose of this progress report is to show the present position and to examine critically the possibilities and limitations of atomic absorption methods.

1. The Physical Principle

To be able to measure the atomic absorption, the sample must be converted into atomic vapor. This step is common to all methods of optical atomic spectroscopy, *i.e.* emission spectral analysis, atomic absorption analysis, and atomic fluorescence analysis.

Atomic absorption is based on the ability of free atoms to absorb electromagnetic radiation of the wavelengths that they are also able to emit. Since the atoms can only pass into certain discrete higher energy states on absorption of radiation energy, they can only absorb radiation quanta that have exactly the energy required for the transition. The absorption spectra of free atoms are therefore line spectra. Atomic absorption, like atomic emission and atomic fluorescence, can be observed only at certain wavelengths that are characteristic of each element. This is the reason for the high selectivity and specificity[1] of atomic spectral methods of analysis, and hence also of atomic absorption methods.

Only the most sensitive lines, *i.e.* the resonance lines, can be used in the main for atomic absorption analysis. These lines are based on transitions from the ground state to an excited state. Some elements, such as titanium, offer a wide selection of lines having similar sensitivities. For other elements, however, there is often only one line that can be used. For example, the zinc lines at 2138 Å and 3076 Å differ by a factor of about 5000 in their sensitivity.

A number of elements cannot be determined with the usual atomic absorption methods and instruments. This is because the resonance lines of these elements, which are indicated by a black triangle in the periodic system in Figure 1, lie in the vacuum UV at wavelengths below 2000 Å. Radiation with wavelengths in this range is unable to penetrate the

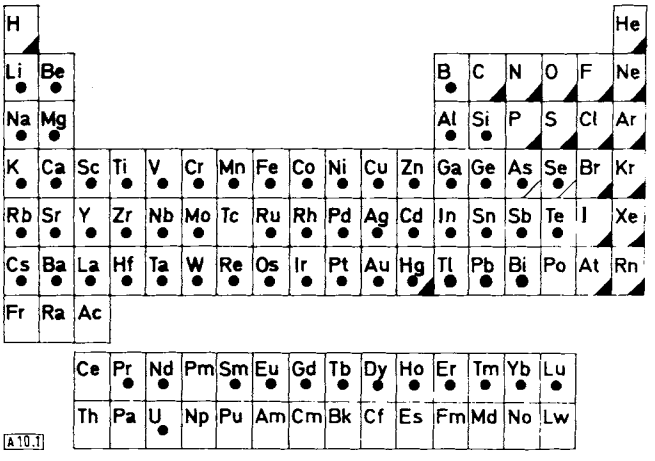


Fig. 1. Periodic system showing the elements that have been determined by atomic absorption with a flame (●), and the elements whose resonance lines lie in the vacuum UV (◢). As and Se are borderline cases.

flame gases and the air. Much more expensive special methods are necessary for the measurement of atomic absorption in this range, but these are not yet of any importance in practical analysis.

However, in the case of mercury, whose most sensitive resonance line is situated at 1850 Å, a less sensitive resonance line at 2537 Å can be used for determination purposes. This

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line is based on a "forbidden transition", *i.e.* a singlet-triplet transition. The determination of mercury with a flame is not very sensitive in this case, but determinations in a simple absorption cell are particularly suitable for mercury. This forms the basis of a series of sensitive methods with high detection powers, which are described in Section 6.

The elements that can still just be determined with a flame and without a vacuum monochromator, though their resonance lines lie below 2000 Å, include arsenic and selenium. The usual flames absorb more than 70% of the radiation at the wavelength of the arsenic line, 1937 Å. Substantially transparent flames, and particularly flames containing no nitrogen, are therefore used for arsenic determinations.

2. Measuring Arrangement and Measuring Principle

The measuring arrangement for atomic absorption analysis is shown in Figure 2. The essential parts are the primary light source (a), the absorption volume (b), the spectral apparatus (c), and the photoelectric measurement and evaluation system (d). The functions of these parts will now be discussed.

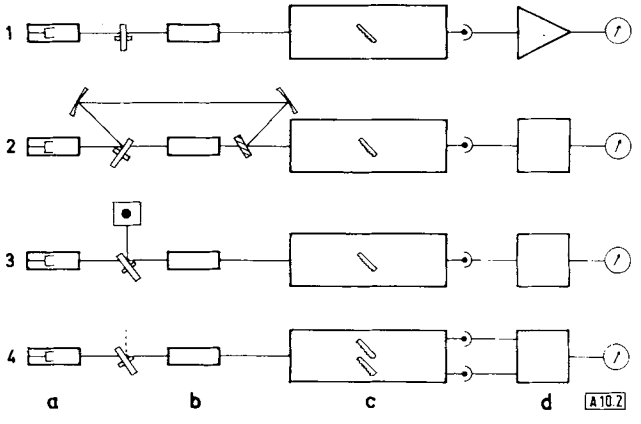


Fig. 2. Diagram of the measuring arrangement of atomic absorption instruments. 1, single-beam instrument; 2, twin-beam instrument; 3, single-beam instrument with automatic background compensator; and 4, twin-channel instrument for simultaneous measurement at two wavelengths. a = primary light source, b = absorption volume, c = spectral apparatus, d = photoelectric measurement and evaluation system (see also Section 2.3).

2.1. Primary Light Sources

To measure the atomic absorption of an element, one must have a primary light source whose emitted radiation has the same wavelength as the resonance line of the element to be analyzed. This requirement is easy to satisfy if one uses a light source that gives a continuous spectrum, *e.g.* an incandescent lamp for resonance lines in the visible region of the spectrum.

However, this is possible only if a spectral apparatus with a very high spectral resolution is used. Normal atomic absorption instruments cannot be used for this purpose, since the width $\Delta\lambda$ of the absorption lines is so small that the lines are extremely difficult or impossible to recognize with moderate spectral resolution. For sensitive measurement, not only should they be recognizable, but it should preferably also be possible to measure the absorption maximum.

As early as 1953—1955, while laying the foundation of atomic absorption spectrometry, *Walsh*[2] showed how very sensitive measurement of atomic absorption could be achieved even with a low spectral resolution, *i.e.* with relatively small instruments; the answer was to use line emitters, particularly hollow

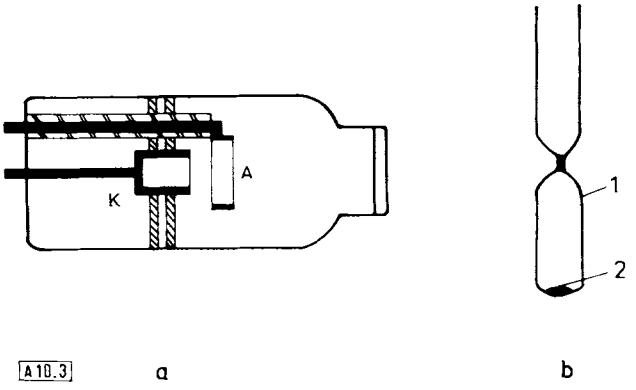


Fig. 3. Primary light sources for atomic absorption spectrometry. a) Hollow-cathode lamp; K = cathode, A = anode. b) Electrodeless quartz lamp for excitation in the high-frequency or microwave range. 1 = Sealed quartz tube, 2 = metal or metal halide.

cathodes (Fig. 3a), as primary light sources. Hollow-cathode lamps emit the line spectrum of the cathode material as well as the line spectrum of the discharge gas.

Under suitable discharge conditions, hollow-cathode lamps emit spectra with very narrow lines, and all that is left to the spectral apparatus is to separate the resonance line from other lines that are not absorbed. It is thus possible to design relatively small, compact atomic absorption instruments. However, interference in the analysis ("spectral interference") is then often unavoidable in the case of spectra containing numerous lines, since the resonance line and the interfering lines cannot be separated completely, if at all.

Another disadvantage is that a different hollow cathode must be used for each element. Though it is possible to construct hollow-cathode lamps (and some are even commercially available) whose cathode material contains several elements, and which therefore emit the spectra of several elements, the number of element combinations that can be used is very limited. Spectra of multielement lamps naturally contain greater numbers of lines, and the danger of spectral interference is therefore increased.

What about the quality of modern hollow-cathode lamps? What other line emitters can be used as primary light sources? Hollow-cathode lamps with a high spectral radiation density at the wavelength of the resonance line have been developed for a large number of elements in recent years. However, they still differ by more than three orders of magnitude in their radiation density. Unfortunately, few reliable measurements have been published[3]. In particular, the hollow cathodes for As, Se, Te, and some rare earth metals are unsatisfactory.

Electrodeless discharge lamps (Fig. 3b) are obtainable for a series of elements. These consist of a sealed quartz tube containing an inert gas at a pressure of a few mbar and some metal or metal halide. The element is vaporized and excited in an alternating electromagnetic field with a high frequency, or in most cases an extremely high (microwave) frequency. These lamps have proved particularly useful in atomic fluorescence analysis.

The requirements for the primary light source are different in fluorescence measurements, since the large solid angle into which these lamps radiate can be utilized in fluorescence excitation. This is not possible in absorption measurements[*]. Practically the only factor that counts in light sources for atomic absorption is the spectral radiation density. However, this is only partly greater for electrodeless discharge lamps than for modern hollow-cathode lamps[3]. In the present state of development, the use of discharge lamps seems worthwhile only for elements for which hollow cathodes with sufficiently high radiation densities are not available, *e.g.* As and Se.

Another important point is the constancy of the radiation emission. The relative standard deviations for the intensity variations are often less than 0.1% for the hollow cathode. This constancy cannot yet be equaled by electrodeless discharge lamps.

Light sources that could become important for atomic absorption spectrometry in the future are variable-frequency lasers[4]. These have high radiation densities and radiate in a very small wavelength range ($\Delta\lambda < 1/100$ Å). There would then be no need for a monochromator. The advantage of these lasers is that the wavelength of their radiation can be varied over a wide range. The same primary light source can therefore be used for the determination of several elements.

However, the tunability is also the weakness of this light source. Since the wavelength is determined by the operating conditions, these conditions must be kept so constant that the variation of the wavelength is considerably less than the width of the emitted wavelength band. This is a great technological problem. Because of the high price of these laser light sources, their use will initially be possible only for special investigations.

2.2. Absorption Volume

For the measurement of the atomic absorption, the sample must be converted as completely as possible into atomic vapor. This is the decisive process. It is this, and not the primary light source, the optics, or the photoelectric measuring technique, that mainly determines the efficiency of the methods.

Flames are used in most cases for the conversion of the sample into atomic vapor, the sample being atomized and introduced continuously into the flame in the form of an aerosol. Very precise concentration determinations are possible by measurement of the atomic absorption with a flame as the absorption volume. Relative standard deviations of 1% can be achieved in many cases. Unfortunately, the detection sensitivity is not high in comparison *e.g.* with that of some methods of emission spectral analysis.

Furnaces are very suitable for use as absorption volumes in microanalyses, and sometimes even for trace analyses. Less common absorption volumes are electric discharges such as DC arcs, high-frequency and microwave plasmas, and hollow cathodes. Unheated or only slightly heated cells are used for mercury determinations.

The special properties of the important absorption volumes will be considered in the discussion of the analytical procedures in later sections.

[*] The relationships for the radiation flux and the optical system are given as an Appendix in the IUPAC Document [13].

2.3. Radiation Selection, Radiation Measurement, and Processing of Experimental Values

In contrast with the methods of emission spectral analysis, whose strength lies especially in the simultaneous determination of several elements (simultaneous analysis with polychromators), the methods used in atomic absorption spectrometry are almost exclusively sequential, *i.e.* the elements are determined one after another. Radiation selection is therefore almost exclusively carried out with monochromators, since the precise determination of several elements with a polychromator would call for a number of conditions that are usually incompatible in practical analytical problems. This will be discussed in Section 4.1.

There are also two-channel atomic absorption spectrometers, which consist of two independent monochromators and measuring systems. However, the importance of these instruments is that the second channel can be used for the measurement of a reference signal rather than to allow the simultaneous determination of two elements. Since the light for both channels is passed through the absorption volume (generally a flame), some types of interference can be almost completely suppressed, while others can be reduced; the types of interference that are affected in this way are those due to processes in the flame.

In all atomic absorption instruments, the radiation of the primary light source is periodically modulated before the absorption volume. This can be achieved by means of a mechanical shutter, *e.g.* by a rotating sector disk (see Fig. 2), or by modulation of the discharge current of the primary light source. This enables the measuring electronics to distinguish between the useful signal coming from the primary light source and the interference signal due to the radiation emission of the flame. This is not entirely possible. In measurements in wavelength ranges in which the flame emits strongly, there is a marked increase in the scatter of the experimental values.

The dark intervals resulting from the modulation of the radiation can be used for the measurement of reference signals to reduce interference. Two such possibilities will be mentioned here.

One possibility is used in twin-beam instruments (Fig. 2, no. 2). On modulation, the beam is not simply interrupted, but is deflected and led around the absorption volume into the monochromator. In this way, lamp fluctuations and fluctuations in the measuring electronics can be reduced, but not fluctuations that arise from the flame, or from the absorption volume in general. After the development of better primary light sources and more stable measuring electronics, however, these more expensive instruments will not necessarily be preferable to single-beam instruments.

A particularly important possibility, on the other hand, is the use of the dark interval for simultaneous background measurement ("background compensation"). During the dark interval of the measuring beam, the light from a second light source, and specificially a source of continuous radiation, *e.g.* a deuterium lamp or an incandescent lamp, is admitted (Fig. 2, no. 3). In this way, the interfering background can be measured and taken into account automatically by electronic means. Since correct measurement of the background is particularly important in atomic absorption spectrometry,

and is also particularly difficult, it will be discussed in Section 4.2.

Modern atomic absorption instruments naturally contain a series of electronic systems designed to allow better and faster collection and processing of the experimental values; these systems will not be discussed here. In any case the necessary critical insight into what happens is not made easier or even superfluous by this.

3. Atomic Absorption Analyses with Flames as Absorption Volumes

3.1. Choice of Flames and Burners

The flames most commonly used in atomic absorption spectrometry are produced with acetylene, propane, or hydrogen as the fuel and air as the oxidizing agent. The acetylene/nitrous oxide flame is also used. Because of their relatively low combustion velocity, these flames can all be produced with an elongated slit burner. This gives a favorable flame shape for absorption measurements. The sample is introduced through a mixing chamber/atomizer. Since the larger droplets of the aerosol (80—90% in most cases) separate out in the mixing chamber, only a very fine aerosol reaches the "laminar" flame. Interference due to incomplete vaporization is therefore less pronounced than in the turbulent flames produced with oxygen as the oxidizing agent and with direct atomizer burners. The properties of some flames are shown in Table 1.

Table 1. Combustion velocities and temperatures of some flames.

Fuel	Oxidizing agent	Combustion velocity [cm/s]	[°C]
Mixing chamber/atomizer and slit burner; laminar flame			
Propane	Air	80	1925
Hydrogen	Air	450	2050
Acetylene	Air	160	2300
Acetylene	Nitrous oxide	180	2900
Direct atomizer burner; turbulent flame			
Hydrogen	Oxygen	3000	2650
Acetylene	Oxygen	2500	3100

The data given (combustion velocities and temperatures) are intended only as a guide. They depend on the conditions under which they were determined[5], *e.g.* on the geometry of the burner and on the fuel gas/oxidizing agent mixture.

Special mention of the acetylene/nitrous oxide flame is appropriate. The introduction of this flame by *Willis* in 1965[6, 7] was probably the most important step in atomic absorption spectroscopy with flames. It allowed the accurate and reliable determination of elements that form very stable compounds (oxides, hydroxides, *etc.*), *i.e.* Al, Be, Ti, B, and rare earth metals. Despite the relatively high temperature of the acetylene/nitrous oxide flame, some elements are converted only very incompletely into atomic vapors. In the case of boron, for example, only 0.3—0.4% of the material is in the atomic form in this flame[8], while in the acetylene/air flame the proportion is less than 0.1%. One disadvantage of the acetylene/nitrous oxide flame is the relatively strong radiation of the flame itself. Because of the very high temperature of the flame, there is a danger of interference due to ionization in the case of readily ionizable elements, since ionized atoms are lost as far as the measurement of the atomic absorption is concerned.

Several, frequently competing requirements must be considered in the choice of flame: high transparency, low intrinsic radiation, high sensitivity, low risk of ionization, low chemical interference (partner effects), *etc.*

An example of a flame with a high transparency, which is particularly important for the determination of elements (such as As and Se) with resonance lines in the short-wave UV, is the argon/hydrogen/diffusion air flame. Air, as the oxidizing agent, diffuses into the flame plasma from outside[9].

3.2. Interference due to Light Scattering and Molecular Absorption[10, 11]

Interference due to light scattering from particles and droplets is particularly noticeable in the short-wave UV. Even if the sample does not contain the element under analysis, this interference may cause an absorption to be recorded on aspiration of the sample. It is then necessary, particularly at low concentrations, to measure the background. This measurement could be carried out with similar samples that contain the element under analysis in an undetectable concentration. If no such samples are available, the background can be determined with a continuous radiation source as the primary light source.

The measurement of the background is much more difficult if it is caused by molecular absorption. Absorption by molecules and free radicals can occur over the entire spectral range. It is caused by molecules and radicals not only from the flame gases but also from the sample matrix. This absorption may occur both in the form of continuous molecular bands and as line-rich electronic excitation spectra. A reliable background measurement free from systematic errors may be impossible in the second case.

3.3. Interference due to Ionization

Interference due to ionization occurs particularly in the determination of elements with low ionization energies, *i.e.* specially in the determination of alkali and alkaline earth metals. As a result of the ionization, some of the atoms are lost as far as the measurement of the atomic absorption is concerned. Some examples showing the content of ionized atoms in some flames are given in Table 2[12]. Varying concentrations of one of these elements may displace the equilibrium between neutral and ionized atoms. If this fact is not taken into account,

Table 2. Content of ionized atoms in relation to the total number of atoms of an element in some flames [12].

Element	Ionization energy	Proportion of ionized atoms [%]		
		Propane/Air	Acetylene/Air	Acetylene/Nitrous oxide
Cs	3.87	28	-	96
Rb	4.16	14	-	90
K	4.32	2.5	-	82
Na	5.12	0.3	-	26
Li	5.37	0.01	-	16
Sr	5.69	-	13	20–80
Ca	6.11	-	3	10–40

the result obtained for the concentration of another element may be wrong. In the determination of easily ionizable elements, therefore, another easily ionizable element, *e.g.* cesium, is generally added as a "spectrochemical buffer"[13] or ionization buffer.

3.4. Chemical Interference

Interference can also occur in the determination of elements because other constituents of the sample form stable compounds with the elements under analysis. An example is the well-known interference due to phosphate in the determination of alkaline earth metals:

$$2CaCl_2 + 2H_3PO_4 + E \rightarrow Ca_2P_2O_7 + 4HCl + H_2O$$

Interference of this kind can be reduced by the addition of *e.g.* an excess of lanthanum chloride:

$$LaCl_3 + H_3PO_4 + E' \rightarrow LaPO_4 + 3HCl$$

where $E' > E$. As a rule, the hotter the flame used, the smaller is the addition required. (In view of the diversity of these interferences, the reader is referred to reviews, particularly in Refs. [14,15].)

3.5. Range of Application of Atomic Absorption Analysis with Flames

It has not yet been possible to determine all the elements whose resonance lines lie in the visible and UV regions of the spectrum. The elements for which this has been possible are indicated in Figure 1. Thus cerium, for example, has not yet been detected by atomic absorption in a flame[16] Cerium oxides, particularly the monoxide, are very stable and do not undergo detectable dissociation even in the fuel-rich reducing acetylene/nitrous oxide flame.

The great sensitivity differences in the determination of the various elements are therefore mainly due to the wide differences in the degree to which the elements can be converted into atomic vapor with the usual flames. Hotter flames, such as electrically produced plasmas[17], may offer important advantages for the determination of some elements.

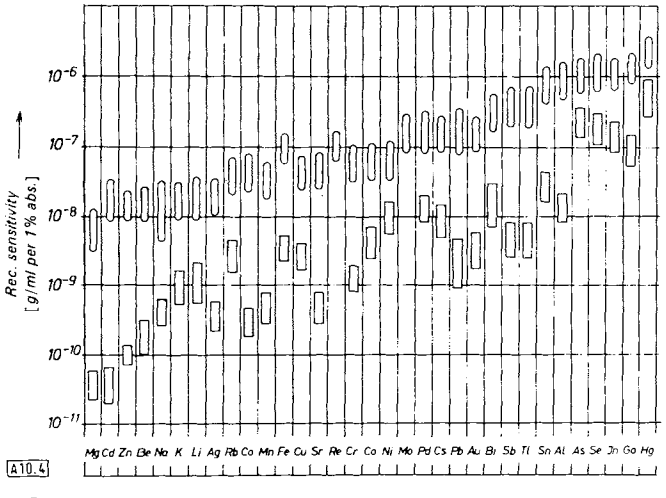


Fig. 4. Approximate ranges for the reciprocal sensitivity in atomic absorption analysis with flames (○) and with graphite tube furnaces (□) (see also Section 5.3).

Figure 4 shows the sensitivities achieved in the determination of a number of elements. The reciprocal sensitivity is plotted in g/ml per 1% absorption[*]. Exact numerical values are meaningless unless the apparatus conditions and the analytical problem are accurately defined; for this reason, the figure shows only ranges. This tells us nothing about the attainable detection limits. These depend not only on the sensitivity but also on the analytical interference level. If the prevailing interferences are due only to the apparatus and the flame, *i.e.* if they are not caused *e.g.* by fluctuating blank values, approximate guide values can be given. Under these (special) conditions, it will be possible to reach detection limits c that are lower than the values indicated for the reciprocal sensitivity c/1% absorption, and in some cases more than an order of magnitude lower.

In addition to the elements indicated in Figure 1 that can be determined directly by atomic absorption, it is also possible to determine other elements by indirect methods. Methods of this kind have been developed *e.g.* for P, S, F, Cl, and I, and also for elements whose direct determination is not sufficiently sensitive, *e.g.* for Ti, V, Nb, Ge, As, and Se. In these methods, use is made of the influence of the element to be determined on another element that can be determined satisfactorily by atomic absorption. For example, fluorine can be determined by measurement of the decrease in the absorption signal of magnesium or the increase in the absorption signal of zirconium[18]. However, special care is necessary in the development of procedures for indirect methods. A survey of these methods is given by *Kirkbright* and *Johnson*[19].

4. Concentration Ranges, Calibration, and Background Measurement in Atomic Absorption Spectrometry

4.1. The Usable Concentration Range

Unlike in the methods of emission spectral analysis, the concentration range in which precise measurements are possible with samples at the same dilution is relatively small in atomic absorption spectrometry. This is true not only of measurements with a flame as the absorption volume, but also for furnace and other methods.

The relative standard deviations for the determination of the concentration of three elements with an acetylene/air flame are plotted against the concentration c in Figure 5. The broken curve shows the effects of fluctuations in the hollow-cathode radiation and in the measuring electronics. These fluctuations are decisive for the large relative standard deviations at low concentrations, but are no longer of any importance at higher concentrations, where the decisive factor is the fluctuations of the concentration of the element under analysis in the flame. However, as can be seen from the standard deviations for absorbance measurements, which are plotted in the same diagram, the relative standard deviations for absorbance measurements are almost constant over a wide absorbance range.

[*] In the literature on atomic absorption spectrometry, data of this type are often referred to as "sensitivity". However, the sensitivity of a method increases as the indicated value in g/ml per 1% absorption decreases. These data are therefore referred to here as "reciprocal sensitivities".

They are about 1% in this case. The rapid increase in the relative standard deviations for the concentration determination at higher concentrations is due not to increasing absorbance fluctuations but to the curvature of the calibration curves. The curvature is particularly pronounced in the case of nickel.

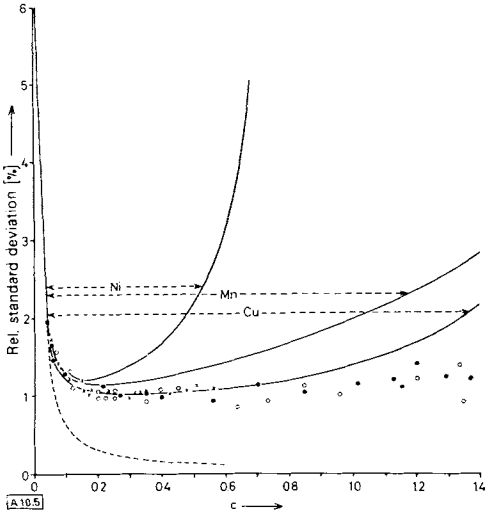


Fig. 5. Usable concentration ranges for the determination of nickel, manganese, and copper by atomic absorption. —·— relative standard deviation for concentration determinations. Relative standard deviation for absorbance measurements of Ni ×, of Mn ○, and of Cu ●. Ni: 2320.0 Å, $F_c = 15$; Mn: 2794.8 Å, $F_c = 35$; Cu: 3247.5 Å, $F_c = 37$. The concentration c is given in arbitrary units.

If one assumes that the relative standard deviation at the limits of the usable range may be twice the value in the most favorable case, the lowest and the highest concentration should differ by a factor of only $F_c = 15$ in the case of nickel, $F_c = 35$ for Mn, and $F_c = 37$ for Cu. The concentration ranges that can be used for precise measurements are therefore only slightly greater than one order of magnitude in atomic absorption measurements.

4.2. Calibration and Background Measurement

As in atomic spectroscopy in general, the calibration must be carried out with "samples of the same type". Calibration samples that have been analyzed by some other method or synthetic samples may be used. Finally, the calibration may also be carried out by the addition method[*]. The choice of calibration method will be decided by the analytical problem.

The condition of calibration with samples of the same type is relatively easy to satisfy if the calibration is carried out by the addition method. However, the results must be regarded particularly critically in this case, since the necessary background measurement can lead to systematic errors in the measurements, even with automatic background compensation.

The problem of the background measurement is to determine the background under the very narrow resonance line, which cannot be resolved by the monochromator. The transmission range of the monochromator is shown as a triangle in Figure 6. The abscissa is the wavelength, and the ordinate is the spectral radiation flux Φ_λ.

The transmission range of the monochromator has a triangular form of this type if the widths of the entry slit and of the exit slit are equal ($s_e = s_a$) and greater than the diffraction width of the monochromator $\lambda f/w$. In this expression λ is the selected wavelength, f is the focal length of the collimator, and w is the size of the beam-limiting diaphragm in the optical system of the monochromator.

In case a (Fig. 6), the radiation flux of the resonance line is decreased by atomic absorption, in case b by continuous background absorption, *e.g.* by the dissociation continuum of molecules, and in case c by a line from the electronic vibrational spectrum of molecules.

If a background measurement is carried out with a source of continuous radiation, the radiation flux will not be measurably reduced in case a, since only atomic absorption occurs. No background absorption will therefore (rightly) be observed. The background measurement also gives the correct value in case b, since the resonance radiation and the continuous radiation are decreased in the same way. In case c, however, the background measurement is wrong, since the resonance line radiation and the continuous radiation are decreased in different ways. This is always so if the background is due to electronic excitation spectra of molecules.

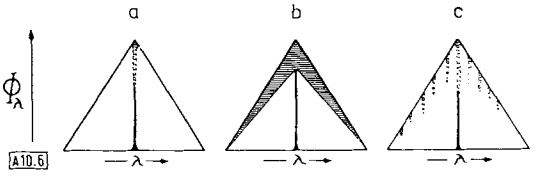


Fig. 6. Decrease in the radiation flux Φ_λ of the resonance line a) by atomic absorption and b) and c) by molecular absorption. The transmission range of the monochromator can be described by $[s_e = s_a \gg \lambda f/w]$. For further details see text.

This is shown in Figure 7 for the background interference of the bismuth line at 3068 Å due to an OH band. The two absorption spectra were recorded with a spectrograph having a very high resolution. In case a, a bismuth solution was

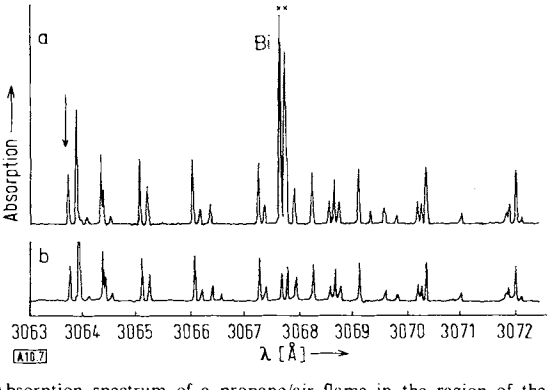


Fig. 7. Absorption spectrum of a propane/air flame in the region of the bismuth line 3067.7 Å. a) With atomic absorption of bismuth, b) without atomic absorption. The arrow indicates the short-wave edge of the OH band. The absorption is given on an arbitrary scale. 3.4 m Ebert spectrograph, grating: 1800 lines/mm, 2nd order spectrum. Practical resolution 250000; photographic recording.

[*] In the addition method (δ calibration [1]), the sample for analysis is divided into portions, and the element to be determined is added to the various portions in stepped known quantities. These samples can then be used as calibration samples for the determination of the course of the analytical curve.

aspirated into a propane/air flame,| while in case b only water was aspirated. As a result of nuclear moment splitting, the bismuth line has two components. It can be seen that two band lines almost exactly coincide with the bismuth lines. The background measurement could be carried out correctly with a spectral apparatus having this resolution. However, this is not possible with the monochromators of moderate resolution that are usual in atomic absorption spectrometry.

5. Atomic Absorption Spectrometry with Furnaces as Absorption Volumes

5.1. Furnace Types and Furnace Methods

The first application of a furnace in atomic absorption spectrometry goes back to *L'vov*. However, the graphite tube furnace developed by this author[20, 21] is very complicated, even after subsequent simplifications[22]. A whole series of simpler furnace types have now become common in analytical practice.

A selection of common furnace types, which differ in the shape and size of the usable absorption volume, is shown in Figure 8. The diagram only shows the main part. Graphite

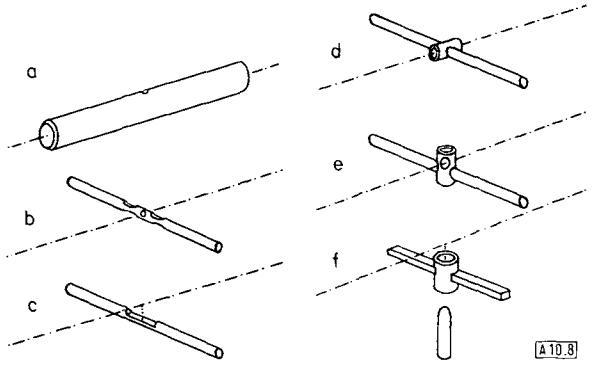


Fig. 8. Furnace types in atomic absorption spectrometry. The optical axis is indicated in each case.

is used as the furnace material. An electric current is passed through the graphite for heating. Temperatures of 2800 °C or higher can be reached in this way within a few seconds.

Electromagnetic high-frequency fields are occasionally used for heating, *e.g.* in the Langmyhr-Thomassen graphite tube furnace[23]. Furnace type f[24] is heated, not by electric resistance heating, but by an arc, which is struck between the lower auxiliary electrode and the graphite crucible.

To prevent combustion of the graphite furnace, it must be used in a chamber filled with inert gas, *e.g.* argon. A chamber of this type is used for the relatively large furnaces of type a[25]. For smaller furnaces, such as types b to e, a stream of inert gas may simply be led over the red-hot graphite[26, 27]

Other materials that are difficult to melt, such as ceramic materials or metals, may naturally also be used as furnace materials. Furnaces with a heatable tantalum strip have proved to be very useful for some analytical problems[28, 29]. A survey was published by *Kirkbright* in 1971[30].

In atomic absorption analyses with flames as absorption volumes, the sample is generally introduced continuously. In spectrochemical terminology, these are known as analyses with "unlimited sample size", The analytical signal is therefore independent of time, and this makes the measurement and averaging very easy. In furnace methods, on the other hand, limited quantities of sample are used in almost every case. A small sample is introduced into the furnace, and the furnace is then heated so that the sample vaporizes as completely as possible. The vapor disappears from the useful absorption volume by diffusion, convection, and possibly by forced flow of protective gas. It is therefore necessary to measure and evaluate a time-dependent signal. Since the magnitude of the analytical signal depends not only on the concentration of the element under analysis but also on the quantity of sample introduced, the quantity of sample must be measured out precisely. This is easy in the case of liquid samples. These generally also satisfy the requirement that the sample introduced should be representative of an initial sample that is usually very much larger.

However, great difficulties often arise in the direct analysis of solid samples, and these may even make the analysis impossible. The division, handling, and introduction of samples that must be smaller (often very much smaller) than 1 mg is difficult, and the danger of contamination is increased. It is also impossible in many cases, *e.g.* in the analysis of geological samples, to ensure that the sample introduced is representative of the larger initial sample[23]. Liquid samples are therefore nearly always used in atomic absorption analyses with furnaces.

5.2. Procedures for Atomic Absorption Analysis with Furnaces

As in all analytical methods, a very carefully devised procedure must be followed in atomic absorption analysis with furnaces. Whereas there have been many investigations on the physical and chemical processes in flames that can be used for this purpose, little is known at present about the decisive processes in atomic absorption furnaces, though systematic studies on this point are in progress at present in several laboratories.

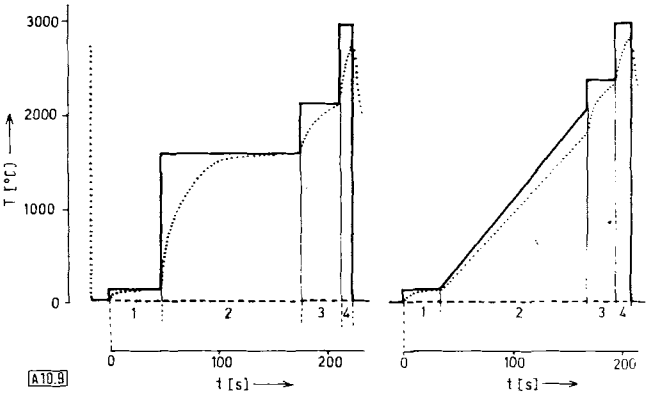


Fig. 9. Heating program for atomic absorption analysis with furnaces. Dotted curves show how the actual temperature follows the set heating program.

In general, the furnace must not be heated immediately to the temperature required to produce the atomic vapor of the element under analysis. Interference due to light scattering and molecular absorption would usually be unavoidable. By trying out suitable heating steps (time) and heating stages (temperature), it is often possible to control the vaporization in such a way that interference due to the sample matrix

is avoided. Figure 9 shows schematic examples of heating programs, which must form an essential part of any procedure.

It is relatively easy to determine the correct heating program for the determination of an element that is difficult to vaporize in a matrix that vaporizes readily. An example is shown in Figure 10. This is the determination of manganese in alkali metal chlorides. The most sensitive resonance line of manganese at 2795 Å lies in a wavelength range in which all alkali metal halides absorb strongly in the vapor phase.

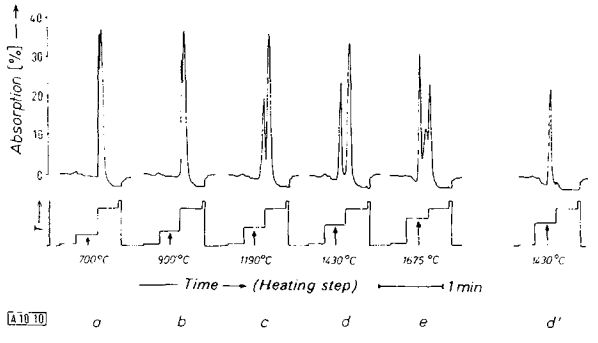


Fig. 10. Experiments for the development of a heating program for the determination of manganese in alkali metal chlorides with a graphite tube furnace (measurements by Dr. Ş. Güçer). For further information see text.

In heating step 1, a final temperature of 110 °C was selected to evaporate the solvent. To establish the temperature that must be selected in heating step 2 to vaporize the alkali metal chlorides without loss of manganese, the temperature was raised in steps from 700 to 1675 °C in experiments a to e. At 1430 °C (experiment d), the background absorption in heating step 2 (1st signal) and the analytical signal in heating step 3 (2nd signal) are clearly separated. A higher temperature in heating step 2 (1675 °C in experiment e) results in loss of manganese at the end of heating step 2.

Experiment d' was carried out under the same conditions as experiment d, but with a deuterium lamp as the primary light source. One therefore sees only the molecular absorption in heating step 2, but not the atomic absorption of manganese in heating step 3.

In many analytical problems it is not so easy to achieve the desired result. A suitable heating program frequently cannot be found. Especially in the trace analysis of organic samples, *e.g.* in biochemical or clinical trace analyses, sample preparation is usually necessary, sometimes at considerable cost. The early hopes of being able to carry out a process equivalent to ashing in the absorption furnace itself have not so far been fulfilled.

It must be pointed out again that the considerations on the background measurement in Section 4.2 also apply to atomic absorption analyses with furnaces. Indeed, automatic background compensation in furnace methods is an important technical aid, without which some analyses would not have been possible. However, its application must be viewed very critically if one is to avoid systematic errors. Unfortunately, there is at present no catalog of interfering molecular spectra and necessary experimental data for atomic absorption analysis with furnaces. A collection of spectra and data of this kind could greatly facilitate the development of reliable procedures.

5.3. Range of Application of Atomic Absorption Analysis with Furnaces

Higher concentrations of atomic vapor are reached in the useful absorption volume of a furnace than in flames. The sensitivity of furnace methods is therefore greater than that of flame methods. A comparison of the reciprocal sensitivities in g/ml per 1% absorption is shown in Figure 4. These were determined with a tube furnace of type a (Fig. 8) having an internal diameter of 8 mm. The sample size was 50 µl. Since the analytical problem cannot be precisely defined here, the diagram once again shows only ranges as a guide to the reciprocal sensitivity.

The furnace methods lose some of their superiority in a comparison of the detection limits. Absorptions lower than 1% can often be measured reliably by flame methods, but only rarely by furnace methods.

This comparison is based on the assumption that sufficient sample material is available for both methods. One advantage of the furnace method, however, is that only small quantities of sample are used (1—100 µl, depending on the type of furnace). The sensitivity and detection power for quantitative analyses of an element are very high. Under favorable conditions, it is possible to determine even 10^{-10}—10^{-11} g of some elements, *e.g.* Mg, Cd, Zn, and Be.

Because of these properties, furnace methods are particularly suitable for the determination of small trace concentrations if a mixed spectrochemical method[31] is used, *e.g.* if a chemical separation or concentration process is carried out first.

How does the detection power compare with that of methods of optical emission spectral analysis? Solid samples were used for this comparison; the concentration data also refer to the mass of the solid substance. A method with a very high detection power was used for comparison[32]; this was emission spectral analysis with a DC arc and a spectrograph whose resolution is so high that the physical width of the lines is resolved.

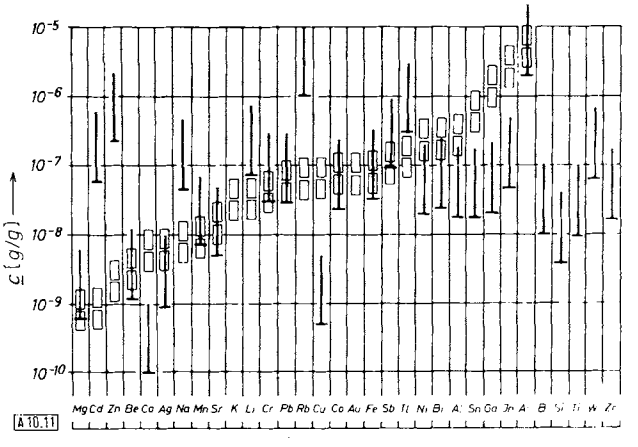


Fig. 11. Approximate ranges for detection limits c in atomic absorption analysis (□) with graphite tube furnace and in emission spectral analysis (⊥) with a DC arc and a high-resolution spectrograph [32].

Here again, naturally, one can only give guiding values unless the analytical problem is accurately defined. Figure 11 therefore shows only ranges. These are valid for cases in which the interference due to the matrix is relatively small. For analyses with the absorption furnace, this means in particular

that only slight interference due to light scattering or molecular absorption occurs in the detection of the element under analysis. As can be seen from Figure 11, by measurement of the atomic absorption in furnaces, it is possible for some elements to reach detection limits of the same order of magnitude as in an emission spectroscopy method with a high detection power, and sometimes, *e.g.* in the case of zinc, to reach even lower limits. This says nothing about whether a particular analytical problem can be solved by one method or by another, but only whether there is any prospect of a solution.

6. Special Methods of Atomic Absorption Spectrometry

In addition to the atomic absorption methods with flames and furnaces, there are a large number of special techniques and methods, which cannot be described in detail here. Some of these are extensions of normal flame methods. Thus the length of the useful absorption volume, and hence the number of free atoms in the absorption volume, can be increased if a flame is allowed to burn in a heated tube through which the radiation passes in the axial direction[33, 34]. This gives a considerably greater detection power for a number of elements[35–38], but the risk of interference is also considerably increased.

The boat method[39] and the method described by *Delves*[40] are also flame methods. In the former, the liquid sample is carefully evaporated to dryness in a metal (*e.g.* tantalum) boat, and the boat is heated rapidly and reproducibly[41] in the flame. As in the furnace methods, a time-dependent absorption signal is then observed. In the Delves method, the sample is evaporated to dryness in a crucible, but its vapor is allowed to flow through a tube that is open in the middle and that is already in the flame. Neither of these methods requires much additional outlay. They are very suitable for a number of analytical problems, *e.g.* for the determination of lead[40] or cadmium[42] in blood. In the simplest case, the sample may even be applied to a sampling loop made from platinum, dried, and vaporized in the flame[43].

Special mention should be made here of the many methods for the determination of mercury[44]. The detection power in the flame is very low, and is inadequate for many analytical problems, particularly for the determination of the element in biological samples and for the checking of environmental pollution.

However, mercury can be determined very satisfactorily in a cold or only slightly heated cell. Methods of this type are now very widely used, and differ mainly in the manner in which the atomic mercury vapor is produced[49, 50].

The method most commonly used at present was developed by *Poluektov*, *Vitkun*, and *Zelyukova*[45]. It is based on the reduction of mercury with $SnCl_2$:

$$Hg^{2+} + Sn^{2+} \rightarrow Hg^{0} + Sn^{4+}$$

The atomic mercury is then transported into the absorption cell in a current of air or nitrogen. A time-dependent signal is generally observed. However, since mercury does not oxidize appreciable in air and condenses only slightly in the concentrations that occur, it is also possible to use closed systems and to measure quasi-stationary absorption signals[46, 47].

This method for the determination of mercury is well suited to automation[48, 49]. However, it is essential that the digestion necessary for the determination in organic samples should be well organized. Since the method for the determination of mercury in the absorption cell has a very high detection power, the practical detection power usually depends on the purity of the reagents required for digestion. *Lindstedt* and *Skare*[49] give a value of 0.5 ng as the detection limit after acid digestion, and 1.5 ng after digestion with permanganate. These detection limits refer to the treatment of ml of urine or 0.3 ml of blood.

7. Closing Remarks—Comparison of the Method of Atomic Absorption Spectrometry with other Spectrochemical Analytical Methods

What do the methods of atomic absorption spectrometry achieve in comparison with other spectrochemical methods of analysis that are also used for the detection of elements and the determination of their concentration? This comparison will be confined to the most important methods of atomic spectroscopy, *i.e.* those of optical emission spectroscopy, X-ray spectroscopy, and mass spectroscopy. Moreover, we can only mention a few very general points that may be important to the assessment or selection of a given method of spectrochemical analysis, since detailed and precise quality figures could be given only if the methods used for the comparison were "complete", *i.e.* if they were defined "by a procedure that is fixed in all its details and by a specific analytical problem"[1].

Let us first consider the state of aggregation of the sample for analysis and the preparation of the sample. For atomic absorption analysis, the samples must be in the liquid form; solid samples must therefore be dissolved. Only a few methods have so far been developed for the atomic absorption analysis of special solid samples.

On the other hand, solid samples are generally used in most other atomic spectrochemical methods, *e.g.* in most methods of optical emission spectral analysis with arcs, sparks, and glow discharges, with those of X-ray spectrometry, and with solid-state mass spectrometry.

If the samples are in the solid form, an analytical method for solid samples can naturally offer considerable advantages. The analysis can sometimes be carried out more rapidly. The monitoring of steel production in a modern oxygen steelworks, for example, is possible only because the steel samples need not be dissolved, but are simply separated and ground after solidification and can then be analyzed, generally with an optical emission spectrometer.

However, the ability to analyze solid samples does not always mean that the sample preparation is simpler and faster. For the geochemical analysis of solid samples, for example, if the analysis is to yield accurate results, a considerable amount of sample preparation is usually necessary, *e.g.* grinding, mixing with additives, melt digestion, *etc.*

Spectral analysis in solution, particularly atomic absorption analysis, may naturally be preferable to solid-state analytical methods purely because the samples are already liquid or because wet-chemical preparations, such as concentration processes, separation processes, *etc.*, are necessary. The form or preparation of the required calibration samples, particularly the preparation of synthetic calibration samples from pure

starting materials, is also much simpler in most cases. The possibility of calibrating an analytical method with synthetic calibration samples (σ calibration[1]) is particularly important in analytical chemistry. With this type of calibration it is possible to obtain analytical results that are free from systematic (but not random) errors, since the true contents are known from the preparation and can be assigned directly to the experimental values. The addition of any necessary additives, such as spectrochemical buffers, is usually also much easier with liquid samples than with solid samples.

Another point that is often of decisive importance in the assessment or selection of spectrochemical analytical methods is the question whether the simultaneous determination of several elements is possible or whether the elements must be determined successively. Simultaneous determinations take less time, at least in photoelectric analytical methods. The quantity of sample required and consumed is generally smaller. It should also be taken into account that in X-ray spectrometric methods of analysis, a certain quantity of sample is necessary, but is not consumed.

Atomic absorption spectrometry is unsuitable for simultaneous determinations of several elements except in very special cases. Most atomic absorption instruments are therefore designed as single-channel instruments. This means that the cost of these instruments is considerably lower than that of optical spectrographs with the accessories for the evaluation of the photographic plate or for spectrometers with photoelectric radiation measurement, *i.e.* instruments that allow the simultaneous determination of several elements.

Provided that a few well-established basic rules are observed, the risk of systematic errors due to interference with the analysis is low. Analyses by atomic absorption spectrometry also have the advantage that they are very precise. Though they frequently do not attain the precision of X-ray spectrometry in the determination of high contents, and sometimes not even that of optical emission spectrometry with photoelectric radiation measurement, the precision is nearly always superior to that of optical emission spectrometry or of mass spectrometry with photographic radiation measurement. The instruments are very simple and flexible. They can be adapted fairly easily for new analytical problems.

These characteristics of atomic absorption spectrometry are the reason why it is used for the analytical problems that call for the precise determination of the concentrations of elements in liquid samples where it is usually necessary to determine only a small number of elements, but possibly in a large number of samples, *e.g.* in medical or biochemical analysis, and where the cost of equipment of such limited problems must be kept low.

However, it is also necessary to point out a disadvantage: the concentrations in liquid samples can be precisely determined only in a relatively small range.

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[1] *H. Kaiser* in *F. Korte:* Methodicum Chimicum. Thieme, Stuttgart, and Academic Press, New York 1973, Vol. 1, Part 1.

[2] *A. Walsh*, Spectrochim. Acta 7, 108 (1955).

[3] *H. Prugger*, Spectrochim. Acta *24 B*, 197 (1969).

[4] *F. P. Schäfer*, Angew. Chem. *82*, 25 (1970); Angew. Chem. internat. Edit. *9*, 9 (1970).

[5] *R. Mavrodineanu* and *H. Boiteux:* Flame Spectroscopy. Wiley, New York 1965.

[6] *J. B. Willis*, Nature *207*, 715 (1965).

[7] *M. D. Amos* and *J. B. Willis*, Spectrochim. Acta *22*, 1325 (1966).

[8] *L. de Galan* and *G. F. Samaey*, Spectrochim. Acta *25 B*, 245 (1970).

[9] *H. L. Kahn* and *J. E. Schallis*, At. Absorption Newslett. *7*, 5 (1968).

[10] *S. R. Koirtyohann* and *E. E. Pickett*, Anal. Chem. *37*, 601 (1965).

[11] *S. R. Koirtyohann* and *E. E. Pickett*, Anal. Chem. *38*, 585 (1966).

[12] *M. Pinta:* Spectrométrie d'absorption atomique. Masson et Cie., Paris 1971.

[13] IUPAC Nomenclature, Units and Their Usage in Spectrochemical Analysis – I. General Atomic Emission Spectroscopy. Vol. 30 (1972).

[14] *J. D. Dean* and *Th. C. Rains:* Flame Emission and Atomic Absorption Spectrometry. Dekker, New York 1969, Vol. I.

[15] *P. Pruvot:* Spectrophotométrie de flammes. Gauthier-Villars, Paris 1972.

[16] *S. R. Koirtyohann* and *E. E. Pickett*, Spectrochim. Acta *26 B*, 349 (1971).

[17] *V. A. Fassel*, Colloq. Spectrosc. Int. 16th, 1971. Adam Hilger, London 1972.

[18] *M. Pinta*, Method. Phys. Anal. *6*, 268 (1970).

[19] *G. F. Kirkbright* and *H. N. Johnson*, Talanta *20*, 433 (1973).

[20] *B. V. L'vov*, Inzh. Fiz. Zh. *2*, 44 (1959).

[21] *B. V. L'vov*, Spectrochim. Acta *17*, 761 (1961).

[22] *B. V. L'vov* and *G. G. Lebedev*, Zh. Prikl. Spectrosk. *7*, 264 (1967).

[23] *F. J. Langmyhr* and *Y. Thomassen*, Z. Anal. Chem. *264*, 122 (1973).

[24] *Yu. I. Belyaev, A. P. Pchelintsev*, and *N. F. Zvereva*, 3rd. Int. Congress on Atomic Absorption and Atomic Fluorescence Spectrometry, Paris 1971.

[25] *H. Massmann*, Spectrochim. Acta *23 B*, 215 (1968).

[26] *M. D. Amos*, Amer. Lab. *1970*, August, p. 33.

[27] *M. D. Amos, P. A. Benett, K. G. Brodie, P. W. Y. Lung*, and *J. P. Matousek*, Anal. Chem. *43*, 211 (1971).

[28] *H. M. Donega* and *T. E. Burgess*, Anal. Chem. *42*, 1521 (1970).

[29] *J. Y. Hwang, P. A. Ullici*, and *S. B. Smith*, Amer. Lab. *1970*, August, p. 41.

[30] *G. F. Kirkbright*, Analyst *96*, 609 (1971).

[31] *L. Pszonicki*, Colloq. Spectrosc. Int. 16th, 1971. Adam Hilger, London 1972, pp. 199—209.

[32] *K. Laqua, W.-D. Hagenah*, and *H. Waechter*, Z. anal. Chem. *225*, 142 (1967).

[33] *K. Fuwa* and *B. L. Vallee*, Anal. Chem. *35*, 942 (1963).

[34] *K. Fuwa, P. Pulido, R. McKay*, and *B. L. Vallee*, Anal. Chem. *36*, 2407 (1964).

[35] *I. Rubeska*, Anal. Chim. Acta *40*, 187 (1968).

[36] *I. Rubeska* and *B. Moldan*, Analyst *93*, 148 (1968).

[37] *B. Moldan*, International Atomic Absorption Spectroscopy Conference, Sheffield 1969. Butterworths, London 1970.

[38] *A. Ando, K. Fuwa*, and *B. L. Vallee*, Anal. Chem. *42*, 818 (1970).

[39] *H. L. Kahn, G. E. Peterson*, and *J. E. Schallis*, At. Absorption Newslett. *7*, 35 (1968).

[40] *H. T. Delves*, Analyst *95*, 431 (1970).

[41] *E. E. Plucker*, At. Absorption Newslett. *8*, 73 (1969).

[42] *R. D. Ediger* and *R. L. Coleman*, At. Absorption Newslett. *12*, 3 (1973).

[43] *R. A. White*, International Atomic Absorption Spectroscopy Conference, Sheffield 1969. Butterworths, London 1970.

[44] *D. C. Manning*, At. Absorption Newslett. *9*, 97 (1970).

[45] *R. A. Vitkun, N. S. Poluektov*, and *Yu. V. Zelyukova*, Zh. Anal. Khim. *25*, 474 (1970).

[46] *H. Brandenberger* and *H. Bader*, Helv. Chim. Acta *50*, 1409 (1967).

[47] *H. Brandenberger* and *H. Bader*, At. Absorption Newslett. *7*, 53 (1968).

[48] *G. Lindstedt* and *I. Skare*, 3rd Int. Congress on Atomic Absorption and Atomic Fluorescence Spectrometry, Paris 1971.

[49] *G. Lindstedt* and *I. Skare*, Analyst *96*, 223 (1971).

[50] *E. Kunkel*, Z. Anal. Chem. *258*, 337 (1972).

Isopeptide Crosslinks—Their Occurrence and Importance in Protein Structure

R. S. Asquith, M. S. Otterburn, and W. J. Sinclair[*]

Isopeptide links refer to bonds between the ε-amino group of lysine and the side-chain carboxyl groups of glutamic or aspartic acid. Covalent crosslinks of this kind, which undoubtedly occur in protein feedstuffs and reduce their nutritional value, also participate in the fibrinogen→fibrin transformation and play a part in stabilizing the structure of keratins. Isopeptide links also arise on heating of both fibrous and globular proteins, the amount formed depending upon the severity of heat treatment. The mode of formation and the significance of these crosslinks require further elucidation.

1. Introduction

Proteins are biopolymers with a molecular weight arbitrarily defined as greater than 5000. They are responsible for many indispensible functions in cellular structure, catalysis, metabolic regulation, and contractile processes, acting in protective and defensive roles in animals.

Protein chains are built up of α-amino acids linked by amido groups (peptide links) between α-amino and α-carboxyl groups of adjacent residues. Many of their properties are dependent, however, not only on this primary sequence of residues in the polypeptide chain but also on the secondary (shape of chain) and tertiary structures (chain aggregation). Many interchenic forces and crosslinks are responsible for maintaining the tertiary structure. These include salt linkages, which are the result of coulombic interactions between oppositely charged acidic and basic side chains and were first postulated in 1931 by *Speakman* and *Hirst*[1] as well as hydrogen bonds, which have also been recognized as not only playing an important role in stabilizing the secondary structure in the normal form of an α-helix, but also occurring as an interchenic link in the tertiary structure[2, 3]. The importance of the interaction between hydrophobic residues in globular proteins was recognized at an early stage[4]. These findings have now been extended to include fibrous proteins[5, 6].

One major naturally occurring covalent crosslink (found particularly in the keratins) is the amino acid cystine, by which two peptide chains can be linked through the disulfide bridge. Because of its ease of oxidation, reduction, and degradation and the influence of these effects on wool keratin, the reactions of the disulfide bridge have been studied particularly thoroughly[6–8]. As a result of this work other crosslinks have been postulated and subsequently isolated from degraded proteins. Thus lanthionine[9, 10], lysinoalanine[11–13], and ornithinoalanine[14] all occur in alkali-treated proteins which in their native form contain cystine. The mechanism of formation is basically a bimolecular β-elimination of a proton in the β-position to the disulfide bond, yielding the reactive intermediate dehydroalanine (Fig. 1).

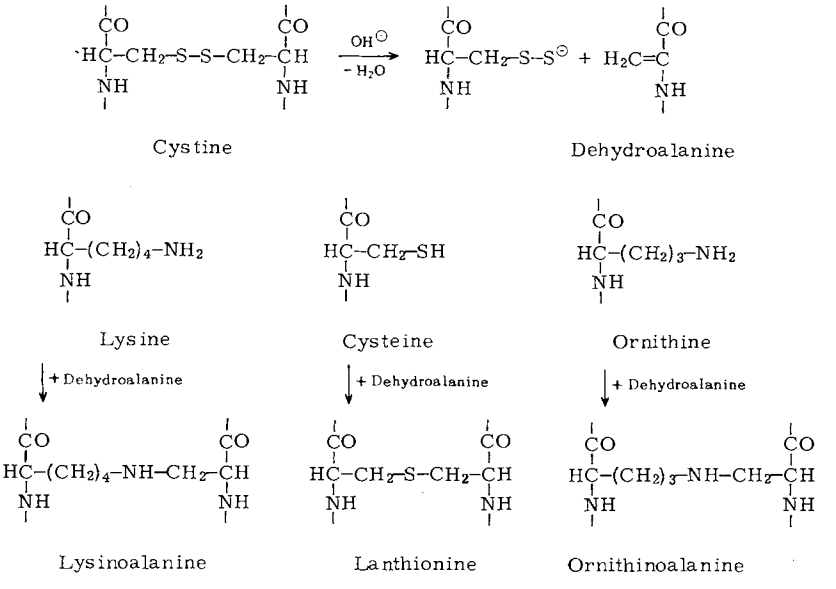


Fig. 1. Formation of dehydroalanine on alkali-treatment of cystine in a protein network; reaction of dehydroalanine to form lysinoalanine, lanthionine, and ornithinoalanine.

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Positive proof of this reaction scheme has recently been obtained by the isolation of the dehydroalanyl peptide: γ-glutamyl-dehydroalanyl-glycine from alkali-treated glutathione[15, 16]. The intermediate so formed can then react with adjacent amino acid residues forming new inter- and intramolecular covalent bonds. Many investigations have shown that increased protein stabilization occurs when such new bonds are formed, and this work has been fully reviewed by *Zahn*[17].

The nature of the crosslinks in collagen and elastin have been presented in a recent review by *Gallop et al.*[18]. Lysine links of dimeric and trimeric tyrosine[20]. The mechanism of formation of the dimer and trimer is believed to be initiated by a peroxidase enzyme. This enzyme catalyzes the oxidative coupling of the tyrosine residues through the position 3 of the aromatic rings. The dimeric and trimeric tyrosines so produced crosslink the polypeptide chain.

Some evidence has recently been put forward by *Raven et al.*[21] that dityrosine occurs in Tussah silk fibroin and wool keratin. No conclusions, however, were drawn by these authors as to whether or not the residue was present as a crosslink.

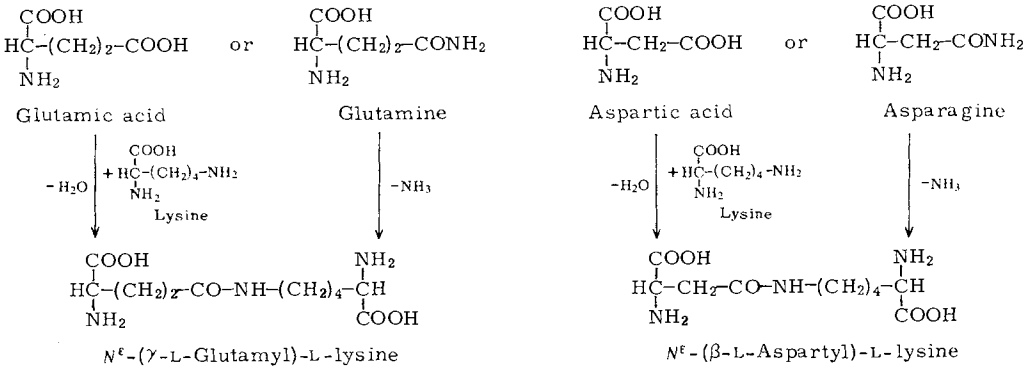
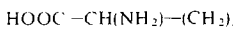
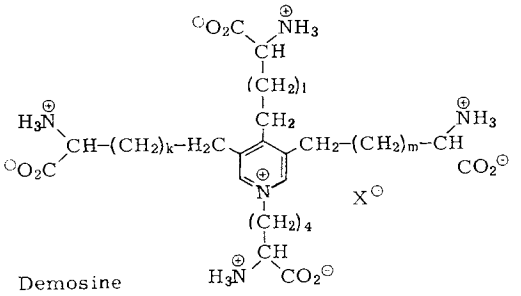


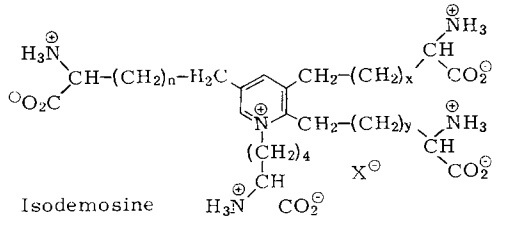
Fig. 2. Postulated reaction schemes for the formation of isopeptides.

is the amino acid primarily involved in such links. This amino acid undergoes enzymic oxidation and deamination yielding 2-aminoadipinaldehydic acid

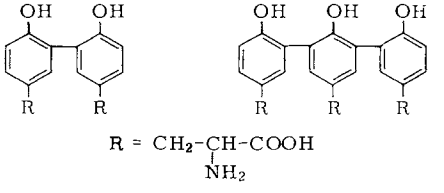


This product is a precursor to the relatively simple crosslinks such as those found in collagen and the more complex ones which occur in elastin, *i.e.* demosine and isodemosine.





The elastic protein resilin, which was isolated from the cuticle of insects by *Weis-Fogh*[19], has been shown to contain cross-



An obvious interaction, which would result in a covalent crosslink being formed, is that between the ε-amino group of lysine and the side-chain carboxylic groups of glutamic or aspartic acids. Loss of water would yield an ω-ε-amide link (Fig. 2). Today such a link is termed an isopeptide link to differentiate it from the normal peptide link.

Whilst such links have often been postulated, only recently have they been established as definite chemical moieties, thereby demanding reinvestigation of many proteins in which their possible occurrence had been ignored. The present paper summarizes some of the more recent findings regarding the isopeptide link.

2. History of the Isopeptide Link

The fact that salt linkages were shown to exist between side chain carboxyl and amino residues as early as 1931 suggested that these groups were sufficiently close to one another to permit the formation of a covalent bond. Such a crosslink was first suggested by *Astbury* in 1934[22] as probably occurring in the keratin molecule. This postulate tended to be obscured by the later findings that lysine reacts with cystine degradation products. Nevertheless, *Pauling* and *Niemann*[23] again suggested in 1939 that the isopeptide link could occur. Indirect evidence accumulated for the formation of the isopeptide link from studies of the effect of heat on proteins; thus *Mecham* and *Olcott*[24] subjected a series of proteins to dry heat and observed that the resulting proteins had decreased solubilities and decreased moisture regain. They also showed that the availability of basic and acidic sites in the heated proteins to dyestuffs had decreased as compared with the unheated material, despite the fact that there was no difference in the amounts of acidic or basic amino acids estimated in hydrolyzates of the materials. *Mecham* and *Olcott* interpreted their

results as a loss of some of these polar groups, possibly by internal ester or amide formation.

Undoubtedly the work of *Beuk et al.*[25] supported the postulate that some form of isopeptide crosslinking was occurring. Thus these authors showed that the digestability of the protein by enzymes decreases as the severity of heating is increased. It has also been noted that some samples of gelatin become insoluble when heated—this has been attributed to isopeptide formation[26], as was the insolubility of anhydrous gelatin[27].

3. Availability of Lysine

From nutritional studies lysine has been known for some time to be an essential amino acid. Indeed it is fairly common to add the free amino acid to protein feedstuffs which are naturally deficient in the compound, in order to enhance their nutritional value.

Heat sterilization can reduce the nutritional value without necessarily reducing the total lysine content of the foodstuff. Undoubtedly many feedstuffs contain carbohydrates as well as proteins, and in the presence of reducing sugars the ε-amino group of lysine can undergo a Maillard reaction, *i.e.* the aldehydic groups of the reducing sugars condense with the ε-amino groups of lysine, thus blocking these groups and rendering the lysine unavailable for nutrition. It was generally and correctly assumed that this type of reaction is responsible for the reduction in the nutritional value of heated foods (*e.g.* dried milk), and may be in part responsible for the color changes observed during heating of foodstuffs.

Carpenter[28] and others[29,30] therefore devised a number of methods of determining the proportion of ε-amino lysine groups available for reaction in foodstuffs and hence nutritionally valuable. These methods rely on reacting the available amino groups of lysine with a reagent such as 1-fluoro-2-4-dinitrobenzene (FDNB). By determining the amount of N^{ε}-(2,4-dinitrophenyl)lysine obtained hydrolysis of the protein and subtracting from the total lysine present, the amount of "bound" lysine is obtained, *i.e.* lysine unavailable for reaction with the reagent. Obviously the ε-amino group of lysine may be blocked by reactions whose products hydrolyze during the hydrolysis of the protein, hence returning this lysine as the free amino acid. Alternatively the ε-amino group may be blocked by the formation of acid-stable products, such as lysinoalanine. The latter products are not returned as lysine on hydrolysis of the protein and may be difficult to detect on amino-acid analysis of hydrolyzates.

Whilst any blocking of the ε-amino group may reduce the nutritional value of the protein, it is sometimes desirable to differentiate between acid-labile and acid-stable link formation. *Asquith et al.*[31] designed a method permitting direct estimation of the "bound" lysine involved in hydrolytically labile links. The method relies on recovery of free lysine following chemical blocking of the available lysine and acid hydrolysis of the protein. Such lysine as is recovered must be that bound by acid-labile links in the protein. These latter authors, however, were not investigating nutritional foodstuffs but rather the effect of dry heat on the carbohydrate-free protein, keratin. Application of this method to the analysis of dry-heated keratin showed that the amount of lysine unavailable for reaction with FDNB, but recoverable as free lysine in the protein hydrolyzate, increases progressively as the severity of treatment increased[32], clearly indicating that acid-labile links are formed on heating keratin.

For the keratins[6] it is well known that selective fission of the disulfide crosslinks by oxidation with organic peroxy acids (*e.g.* performic acid) results in a material separable into three fractions by isoionic precipitation. These fractions are termed α-keratose (soluble in alkali, insoluble in acid), β-keratose (insoluble in acid or alkali), γ-keratose (soluble in acid or alkali at all pH values). The fission of the disulfide bonds thus increases the solubility of keratin in suitable aqueous solvents.

Increased solubility by reduction of the degree of interchenic crosslinking is a common phenomenon in polymer chemistry. Even though it has been suggested that these fractions correspond, in untreated wool, to specific histological components of the fiber, decreases in solubility can still be used[33] as a measure of enhanced crosslinking (caused by introduced links stable to peroxy acids). Prior heat treatment of the wool resulted in an increase in the proportion of the insoluble fraction (modified β-keratose), with a corresponding decrease in the more soluble fraction. The more prolonged or intense the heat treatment, the greater is the degree of insolubilization of the protein. This clearly indicates progressive enhancement of crosslinking of some type by the heat treatment.

Examination of the fractions obtained from different wools indicated that the proportion of bound lysine is greatest in the insoluble β-keratose fraction, even in untreated wool. Further, the proportion of bound lysine increases with severity of heat treatment (Fig. 3). The proportion of bound lysine in the more soluble fraction α-keratose remained the same, irrespective of heating conditions[32]. The amount of this fraction decreases as severity of treatment increases, suggesting that when crosslinking through lysine reaches a certain level this fraction becomes insoluble in ammonia solution. The most soluble fraction (γ-keratose) contains a negligible proportion of bound lysine which is unaffected by heat treatment, although the proportion of the fraction changes.

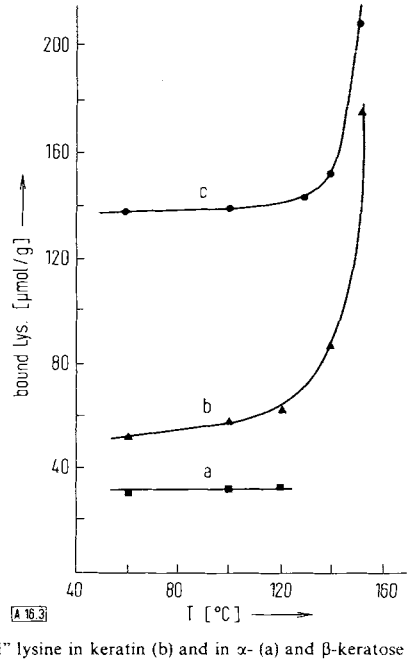


Fig. 3. Amount of "bound" lysine in keratin (b) and in α- (a) and β-keratose (c) *versus* the temperature of heating. The samples were heated for 48 h.

These results not only clearly indicate that interaction of lysine with some other amino acid to yield an acid labile link is occurring in keratin, but also show that the product of this reaction acts as an interchenic crosslink. This was further substantiated in the case of heated keratin by the finding that there is a direct relationship between the proportion of insoluble β-keratose fraction found and the concentration of "bound" lysine present, as shown in Figure 4. Even

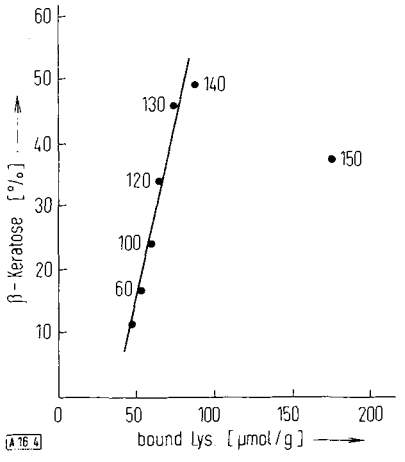


Fig. 4. Amount of insoluble β-keratose *versus* the concentration of bound lysine. The numbers indicate the temperature [°C] at which the samples were heated. The lowest point corresponds to a control sample.

in the β-keratose fraction obtained from virgin wool there is a markedly greater proportion of "bound" lysine than in either of the other fractions from the same source. On the basis of these findings *Asquith* and *Otterburn* postulated the possibility of isopeptide bonds[32] being the acid-labile crosslink formed. Further, *Bjarnason* and *Carpenter*[34, 35] showed that after heat treatment the available lysine decreases in pure nutritional proteins and postulated the occurrence of the isopeptide links as being responsible. Despite these numerous postulates, conclusive proof of the existence of such links was difficult to obtain.

4. The Isopeptide Link in Fibrin

It was in this field of research that the first breakthrough in the identification of an isopeptide link was achieved. Early workers on the fibrinogen→fibrin transformation had suggested the free glycine end groups react with glutamic acid to give γ-glutamyl-glycine links which would lead to the fibrinogen becoming insoluble[36], this reaction being catalyzed by a transglutaminase. In 1966, however, *Lorand*[37] postulated the formation of N^{ε}-(γ-glutamyl)-lysine isopeptide, as did *Fuller* and *Doolittle*[38], to account for the insolubility of fibrin.

The major difference between this work and that on heated proteins was the mechanism proposed for the formation of the isopeptide link. Thus it was assumed that the link in heated proteins results from a condensation reaction between the free carboxyl of glutamic acid and the ε-amino group of lysine with loss of water, whereas in the fibrinogen→fibrin transformation such a dehydration reaction would be less likely *in vivo*. Hence linkage was postulated to occur through an amide exchange between glutamine and an ε-amino group of lysine. Such a reaction would be more probable in enzyme-catalyzed systems.

It was not until 1968 that three groups of workers advanced more definite evidence of the existance of the N^{ε}-(γ-glutamyl)-lysine crosslinks in polymerized fibrin[39–41]. These workers found that crosslink formation in the fibrinogen→fibrin transformation involves a complex series of reactions; firstly thrombin causes the splitting off of fibrinopeptides A and B from fibrinogen, yielding a fibrin gel which is then strengthened by isopeptide crosslinking. The reaction is catalyzed by transglutaminase enzyme *in vivo*. The same authors also examined whether N^{ε}-(β-aspartyl)-lysine isopeptide crosslinks might also be present. However, available evidence suggests that this isopeptide is absent in fibrin.

5. Isopeptides in Virgin Wool

The major difficulty in the identification and isolation of a moiety such as the isopeptide link in keratin is that it cannot be isolated by acid hydrolysis. Enzymic hydrolysis of keratin is also difficult due to the high concentration of cystine residues in the proteins, thus preventing easy penetration of enzymes into the insoluble matrix. Positive identification of isopeptides was therefore impossible until a system of total enzyme hydrolysis suitable for keratin had been devised. In 1969 such a method was developed at WIRA (Wool Industries Research Association)[42]. The method consists of first reducing the cystine residues with tributylphosphane and blocking the thiol groups so formed by reaction with acrylonitrile, to prevent reoxidation. The fibrous protein is therefore opened up to subsequent attack by enzymes and can be hydrolyzed completely to amino acids by treatment with pepsin, pronase, amino peptidase M, and prolidase[43]. These enzymes together catalyze the hydrolysis of all normal peptide links along the chain but do not attack the primary amido groups of asparagine or glutamine, nor are the isopeptide links of N^{ε}-(γ-glutamyl)-lysine or N^{ε}-(β-aspartyl)-lysine affected. Prior to the publication of the hydrolytic system a cooperative study was undertaken by *Asquith* and *Otterburn* and the WIRA group. This work resulted in the identification and isolation of N^{ε}-(γ-glutamyl)-lysine in virgin wool keratin[44].

Whilst in work with other proteins the isopeptide link had been detected by comparison of enzyme hydrolyzates with synthetic N^{ε}-(γ-glutamyl)-lysine, this was the first time that the isopeptide N^{ε}-(γ-glutamyl)-lysine was positively identified. Examination of enzyme hydrolyzates obtained from virgin wool indicated two peaks in the region between leucine and tyrosine—one of which corresponds in mobility to N^{ε}-(γ-glutamyl)-lysine (Fig. 5).

Using a preparative ion-exchange column a wide fraction was collected containing leucine, tyrosine, and the two unknowns. After desalting and concentration, this fraction was separated by paper chromatography. Using synthetic N^{ε}-(γ-glutamyl)-lysine as a marker, the band corresponding in position to the isopeptide was excised and eluted with distilled water. The eluate was split into two portions, the first of which was acid-hydrolyzed and found to contain not only glutamic acid and lysine but also aspartic acid.

The second portion was treated with 5-dimethylamino-1-naphthalenesulfonyl chloride (DNS). On subequent acid hydrolysis

this portion yielded α-DNS-Asp, α-DNS-Glu, and α-DNS-Lys. The presence of α-DNS-Lys indicated that the ε-amino group was blocked in the original peptide material, whilst the presence of α-DNS-Asp and α-DNS-Glu indicated that their α-amino groups were not involved in peptide links. Thus it was possible to conclusively establish the presence of both types of isopeptide links[45].

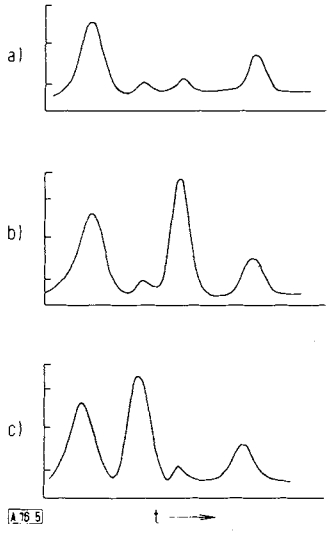


Fig. 5. Chromatograms of a) enzymically hydrolyzed wool keratin, b) with addition of synthetic N^{ε}-(γ-glutamyl)-lysine, and c) with addition of synthetic N^{ε}-(β-aspartyl)-lysine.

In both this work and work by *Milligan et al*[46] the amounts of N^{ε}-(γ-glutamyl)-lysine present in virgin wool were found to be very small. *Harding* and *Rogers*[47] found considerably greater amounts of the isopeptide in the keratin spines of various mammals. *Loewy et al.* reported N^{ε}-(γ-glutamyl)-lysine in the cultures of chicken-breast muscle and L-cell membrane[48]. Examination of oxidized wool keratin by *Asquith et al.*[49] indicated that the insoluble fraction (β-keratose), believed to arise from the inter-cuticular membrane[33], had the highest concentration of isopeptide links. The helix material (α-keratose) contained less whilst the amorphous γ-keratose contained none.

These findings open up fields for discussion on the importance of this link in maintaining the physical properties of structural proteins. Whilst in the fibrinogen→fibrin transformation its function may be to assist in the insolubilization of the fibrin, and it may also assist a similar function in muscle protein, its importance is less well defined in the fibrous proteins. Certainly the keratins after keratinization are well stabilized in their physical form by the disulfide bonds. The isopeptide links present in them may be purely fortuitous as a result of earlier metabolic processes prior to the formation of the fiber. Alternatively, *Otterburn*[50] pointed out that the formation of the disulfide crosslinks (*i. e.* keratinization) of the wool fiber occurs at a relatively late stage in fiber formation and he therefore suggested that the isopeptide links, though few in number, may stabilize the protein prior to keratinization into a less mobile and less soluble form. Their presence may permit an easier alignment of the material during extrusion into the follicle and also aligning the sulfydryl residues in suitable positions for easy oxidation to the disulfide bonds.

Zahn[51], in an excellent summary on the importance of crosslinking in the structure of keratin fibers, drew attention to the slightly different view adopted by *Harding* and *Rodgers*[47]. These authors, in their studies of the isopeptide content of a series of mammalian fibers, of which foetal lamb's wool was one, showed that those fibers exhibiting a high content of medulla tended to have a high isopeptide content. They therefore postulated that the disulfide bond is of prime importance in stabilization of the cortex, but suggested that the isopeptide link may be of more significance in stabilizing the protein of the medulla. Such postulates must at this stage remain very tentative.

6. Isopeptide Formation in Heated Wool

Asquith and *Otterburn* were able to show that on dry heating of wool the concentration of isopeptide links increased considerably (Table 1)[49]. Thus, whilst in virgin wool only very small amounts of N^{ε}-(β-aspartyl)-lysine were found, the quantity virtually doubled after heating for 48 h at 120 °C. Clearly both types of isopeptide links are being formed in the heating process and, since ammonia is lost, this may occur *via* direct dehydration or amide exchange (see Fig. 2). These authors reported that when wool keratin is heated at temperatures above 140 °C for prolonged times the protein remains resistant to enzymatic hydrolysis even after complete reduction of the disulfide bonds. They had previously observed[31] that the bound lysine in such samples, as determined with 1-fluoro-2,4-dinitrobenzene, was high. They could only conclude that considerable isopeptide crosslinking had occurred and this was sufficient to inhibit enzyme-catalyzed hydrolysis.

Table 1. Isopeptide content [μmol/g] of heated wool keratin. The lysine content amounts to 220 μmol/g, the duration of heating 48 h.

T [C]	"Bound" Lys	N^{ε}-(γ-Glu)-Lys	N^{ε}-(β-Asp)-Lys
—	45	15	13
60	50	17	17
100	55	20	20
120	60	25	20
140	90	40	35

Such an inhibition could arise if the protein was becoming more highly crystalline, and hence preventing the penetration of the enzymes. Studies of the changes in the X-ray diffraction pattern of heated wools[52] does not support such a hypothesis. The ordered structure (observed as the α-pattern of keratin) commences to decay in material that has been heated to above 140 °C, the reflections then becoming less discrete until a totally amorphous material is finally abtained. This change, by opening up of the crystalline structure, would be expected to enhance ease of penetration rather than the converse, thus assisting enzyme-catalyzed hydrolysis. It was therefore concluded that the high degree of crosslinking by isopeptide links is responsible for the resistance to hydrolysis. The three-dimensional polymer so produced presumably excludes the approach of the enzyme molecules to the normal labile peptide bonds by a pore-sieve effect.

Such findings are of only academic significance in relation to changes in the structure of wool keratin, precluding as they do an absolute estimation of the amounts of isopeptide

links formed in vigorously heated wool. In relation to digestibility of nutritional proteins, however, such enzyme resistance could be of practical significance. It would seem improbable that a protein changes suddenly from an easily hydrolyzed, slightly crosslinked material to a totally enzyme resistant, highly crosslinked substance. It is more likely that enzyme hydrolysis is progressively retarded as crosslinking increases until a point is reached where no hydrolysis occurs. The possible effects of such factors on nutritional studies are discussed below.

7. Significance of Isopeptides in Nutrition

It is now well established that the nutritional value of protein feedstuffs is reduced on heat sterilization. Since *Carpenter*[53] and other workers[54, 55] have conclusively established that this fall is accompanied by an increase in the binding of the ε-amino group of lysine, as determined by the 1-fluoro-2,4-dinitrobenzene technique, it is clear that this ε-amino group is essential in some way in the metabolism of nutritional proteins. The simple blocking of lysine side chains by acetylation is insufficient to explain the reduction in nutritional properties of lysine-containing protein feedstuffs, for *Bjarnason* and *Carpenter*[34] showed that N^{ε}-acetyl-L-lysine has the growth promoting value of an equivalent quantity of L-lysine when fed to young rats in a lysine-deficient diet. Further, total acetylation of the ε-amino group of lysine in a protein feedstuff does not reduce the growth promoting factor as much as an absence of lysine. Feeding of heated protein foodstuff also leads to a greatly increased amount of fecal lysine.

In a study of the effect of heat damage of proteins *Bjarnason* and *Carpenter*[35] concluded that the reaction of the ε-amino groups of lysine with the γ- and β-carboxyl group of glutamic and aspartic acids respectively could occur under drying conditions encountered in practice. They therefore suggested that lysine may be bound by isopeptide links or by the decomposition products of cystine—the latter would result in the formation of lanthionine and lysinoalanine, as has been shown in other proteins[56].

Recently *Waible* and *Carpenter*[57] investigated the influence of N^{ε}-(γ-glutamyl)-lysine on the growth of chicks and were able to show that the free isopeptide is undoubtedly metabolized and has some growth promoting effect. None of the peptide could be detected in the urine although some occurred in the plasma, indicating absorption of the material through the intestine wall.

Further work has shown the difficulty of this problem. Thus it has been shown with chicken muscle protein that the amount of unavailable lysine increased on sterilization whilst the nutritional value decreased. Further, as the amount of cystine present in chicken muscle is small, it is hardly surprising that neither lysinoalanine nor lanthionine were detected in the acid hydrolyzates. Subsequent analyses for isopeptides have conclusively proven the occurrence of isopeptides in the heated material. The isopeptide was formed in inverse proportion to the amount of available lysine present[58].

Investigation of the amounts of isopeptide links in the feces and urine of rats fed on this sterilized protein show that no compounds having isopeptide links are detectable in the urine or in low molecular weight peptides therein. However, on enzyme hydrolysis the fecal protein has been shown to contain N^{ε}-(γ-glutamyl)-lysine and N^{ε}-(β-aspartyl)-lysine. The amounts present are considerably less than are present in the dietary protein, clearly indicating that breakdown of the isopeptide link can occur in the digestive tract.

The mere chemical fixation of the ε-amino group of lysine in this protein is not, therefore, the sole reason for the loss in nutritional value. It would seem that the formation of these crosslinks (as was found previously with heated wool) is sufficient to retard enzyme degradation of the protein such that at least part of it passes beyond that part in the digestive system where easy absorption into the blood stream is possible. Although analyses have shown that the proportion of isopeptide crosslinks in the feedstuff has decreased by the time the material arrives in the ileum, this decrease is considerably less than that observed when the material passes from the ileum to the colon[58]. This latter degradation of the protein and isopeptide link may occur *via* such processes as fermentation in the hind gut; however, absorption is then reduced to such an extent that an overall loss in nutritional value is still observed. Further elucidation of these theories is being carried out.

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[1] *J. B. Speakman* and *M. C. Hirst*, Nature *128*, 1073 (1931).
[2] *A. E. Mirsky* and *L. Pauling*, Proc. Nat. Acad. Sci. USA *22*, 439 (1936).
[3] *G. C. Pimentel* and *A. L. McClellan*: The Hydrogen Bond. Freeman, San Francisco 1960.
[4] *I. M. Klotz*, Brookhaven Symp. Biol. *13*, 25 (1960).
[5] *H. Zahn*, Palette *21*, 19 (1965).
[6] *W. G. Crewther, R. D. B. Fraser, F. G. Lennox*, and *H. Lindley*, Advan. Protein Chem. *20*, 191 (1965).
[7] *P. Alexander, R. F. Hudson*, and *C. Earland*: Wool. Its Chemistry and Physics. Chapman and Hall, London 1963.
[8] *R. Cecil* and *J. R. McPhee*, Advan. Protein Chem. *14*, 255 (1959).
[9] *J. B. Speakman* and *C. S. Whewell*, J. Soc. Dyers Colour. *52*, 380 (1936).
[10] *M. J. Horn, B. B. Jones*, and *S. J. Ringel*, J. Biol. Chem. *138*, 141 (1941).
[11] *Z. Bohák*, J. Biol. Chem. *239*, 2878 (1964).
[12] *A. Patchornik* and *M. Sokolovsky*, J. Amer. Chem. Soc. *86*, 1860 (1964).
[13] *K. Ziegler*, J. Biol. Chem. *239*, P.C. 2713 (1964).
[14] *K. Ziegler*, Nature *214*, 404 (1967).
[15] *R. S. Asquith* and *P. Carthew*, Biochim. Biophys. Acta *278*, 346 (1972).
[16] *R. S. Asquith* and *P. Carthew*, Tetrahedron *28*, 4769 (1972).
[17] *H. Zahn, H. Beyer, M. M. Hammoudeh*, and *A. Schalla*, Melliand Textilber. *50*, 1391 (1969).
[18] *P. M. Gallop, O. O. Blumenfeld*, and *S. Seifter*, Annu. Rev. Biochem. *41*, 617 (1972).
[19] *T. Weis-Fogh*, J. Exp. Biol. *37*, 889 (1960).
[20] *S. O. Andersen*, Biochim. Biophys. Acta *93*, 213 (1964).
[21] *D. J. Raven, C. Earland*, and *M. Little*, Biochim. Biophys. Acta *251*, 96 (1971).
[22] *W. T. Astbury* and *H. J. Woods*, Phil. Trans. Roy. Soc. London *A 232*, 333 (1934).
[23] *L. Pauling* and *C. Niemann*, J. Amer. Chem. Soc. *61*, 1860 (1939).
[24] *D. K. Mecham* and *H. S. Olcott*, Ind. Eng. Chem. *39*, 1023 (1947).
[25] *J. F. Beuk, F. W. Chornock*, and *E. E. Rice*, J. Biol. Chem. *60*, 291 (1948).
[26] *J. Bello* and *H. Riese-Bello*, Sci. Ind. Photogr. *29*, 361 (1958).
[27] *I. V. Yannas* and *A. V. Tobolosky*, Nature *215*, 507 (1967).
[28] *K. J. Carpenter*, Biochem. J. *77*, 604 (1960).
[29] *S. R. Rao, F. L. Carter*, and *V. L. Frampton*, Anal. Chem. *35*, 1927 (1963).
[30] *L. Blorm, P. Hendricks*, and *J. Caris*, Anal. Biochem. *21*, 491 (1967).
[31] *R. S. Asquith, D. Chan*, and *M. S. Otterburn*, J. Chromatogr. *43*, 312 (1969).
[32] *R. S. Asquith* and *M. S. Otterburn*, J. Text. Inst. *61*, 569 (1970).

[33] *R. S. Asquith* and *D. C. Parkinson*, Text. Res. J. *34*, 1064 (1966).

[34] *J. Bjarnason* and *K. J. Carpenter*, Brit. J. Nutr. *23*, 859 (1969).

[35] *J. Bjarnason* and *K. J. Carpenter*, Brit. J. Nutr. *24*, 313 (1970).

[36] *L. Lorand, K. Konishi*, and *A. Jacobsen*, Nature *194*, 1148 (1962).

[37] *L. Lorand, H. H. Ong, B. Lipinski, N. G. Rule, J. Downey*, and *A. Jacobsen*, Biochem. Biophys. Res. Commun. *25*, 629 (1966).

[38] *G. M. Fuller* and *R. F. Doolittle*, Biochem. Biophys. Res. Commun. *25*, 694 (1966).

[39] *S. Matacice* and *A. G. Loewy*, Biochem. Biophys. Res. Commun. *30*, 356 (1968).

[40] *J. J. Pisano, J. S. Finlayson*, and *M. P. Peyton*, Science *160*, 892 (1968).

[41] *L. Lorand, J. Downey, T. Goton, A. Jacobsen*, and *S. Tokura*, Biochem. Biophys. Res. Commun. *31*, 22 (1968).

[42] *J. C. Fletcher*, personal communication (Jan. 1969).

[43] *M. Cole, J. C. Fletcher, K. L. Gardner*, and *M. C. Corfield*, Appl. Polym. Symp. *18*, 147 (1971).

[44] *R. S. Asquith, M. S. Otterburn, J. H. Buchanan, M. Cole, J. C. Fletcher*, and *K. L. Gardner*, Biochim. Biophys. Acta *207*, 342 (1970).

[45] *R. S. Asquith, M. S. Otterburn*, and *K. L. Gardner*, Experientia *27*, 1388 (1971).

[46] *B. Milligan, L. A. Holt*, and *J. B. Caldwell*, Appl. Polym. Symp. *18*, 113 (1971).

[47] *H. W. H. Harding* and *G. E. Rodgers*, Biochim. Biophys. Acta *257*, 37 (1972).

[48] *A. G. Loewy, S. S. Matacis*, and *M. Showe*, Fed. Proc. *30* (Part 2), 1299 (1971).

[49] *R. S. Asquith* and *M. S. Otterburn*, Appl. Polym. Symp. *18*, 277 (1971).

[50] *M. S. Otterburn*, Ph. D. Thesis, University of Bradford (England) 1970.

[51] *H. Zahn*, Palette *42*, 29 (1973).

[52] *R. S. Asquith, M. S. Otterburn*, and *J. A. Swift*, J. Text. Inst. *63*, 544 (1972).

[53] *K. J. Carpenter*, Nutr. Soc. Eng. and Scot. *17*, 91 (1958).

[54] *C. H. Lea* and *R. S. Hannah*, Biochim. Biophys. Acta *4*, 1950 (1950).

[55] *K. M. Henry* and *S. K. Kon*, Biochim. Biophys. Acta *5*, 455 (1950).

[56] *R. S. Asquith* and *M. S. Otterburn*, J. Text. Inst. *60*, 208 (1969).

[57] *P. E. Waible* and *K. J. Carpenter*, Brit. J. Nutr. *27*, 509 (1972).

[58] *R. S. Asquith, M. S. Otterburn, W. J. Sinclair, K. J. Carpenter*, and *R. Hurrel*, unpublished results.

Halovinylene Carbonates in Organic Synthesis

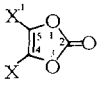
New synthetic methods (2)

By Hans-Dieter Scharf[*]

Monohalo- and dihalovinylene carbonates constitute a new class of cyclophiles which permit simultaneous introduction of masked α-hydroxyketo and α-diketo functions, respectively, into the cycloadducts. Demasking can be performed by simple hydrolysis. Solvolytic opening of the carbonate ring leads to glycolic acid derivatives in the case of the monohalo compounds and to glyoxylic acid derivatives with the dihalo compounds. Preparation of the title compounds, their potential as synthetic reagents, and the chemistry of their simple reaction products are surveyed from a preparative viewpoint.

1. Introduction

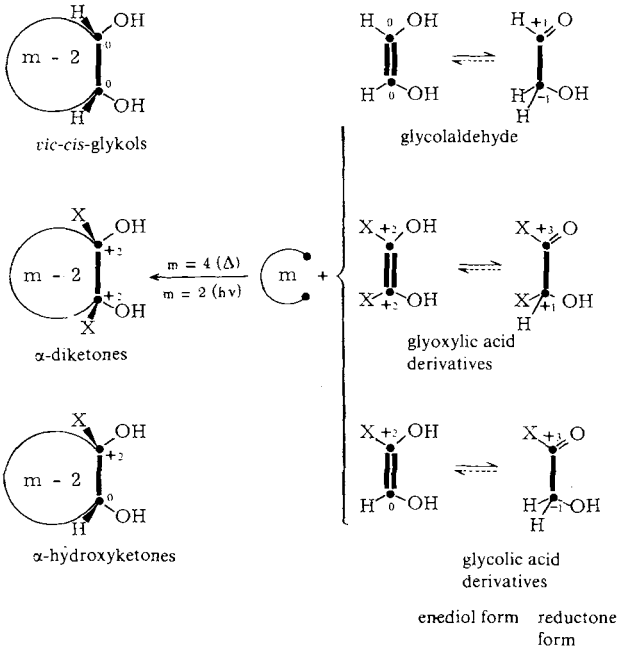
Vinylene carbonate (1,3-dioxol-2-one) *(1)*, the parent compound of the class, has been known since 1953[1], and its behavior as a reactant in both thermal[2-9] and photochemical cycloadditions[10-15] has been repeatedly investigated.



(1), X = X' = H
(2), X = X' = Cl
(3), X = Br, X' = H
(4), X = Cl, X' = H
(5), X = X' = Br

Compound *(1)* is the cyclic carbonate of the *cis*-enediol form of glycolaldehyde. The oxidation states of the two carbon atoms, which differ in the reductone form of glycolaldehyde[16] (+1 and −1), become equal in the tautomeric enediol form; cycloaddition to an *m*-centered π-electron system yields an adduct exhibiting the oxidation pattern of a vicinal *cis*-diol.

Formal replacement of two hydrogen atoms of glycolaldehyde by halogen X raises the oxidation states of the two C atoms



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by two, both in the reductone form and in the enediol form. Cycloaddition reactions then furnish adducts having the oxidation pattern of an α-diketone. These compounds can be liberated by solvolysis.

Finally, a tautomeric enediol form is also conceivable for corresponding derivatives of glycolic acid with differing oxidation states (+2 and 0) at the two centers, which—being fixed by the carbonate ring as in the other cases—confer the oxidation pattern of an α-hydroxy ketone upon the cycloadduct. This formalism provides a satisfactory description of the chemistry of the vinylene carbonates *(1)*—*(5)*. Two-center attack at positions 4 and 5 in *(1)*—*(5)* leads to derivatives of the enediol form, while nucleophilic attack at position 2 affords derivatives of the reductone form[*].

Hence vinylene carbonates are versatile reagents for the preparation of substances which are accessible only with difficulty, if at all, by other routes.

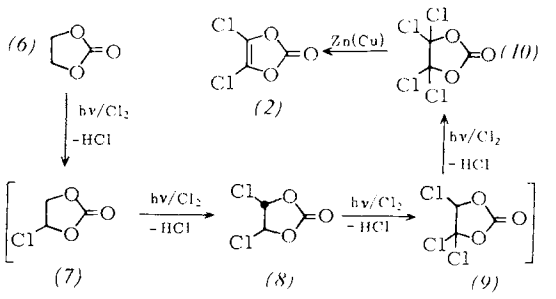
The present progress report surveys the (mainly preparative) results obtained so far with the derivatives *(2)*—*(5)*.

2. Preparation and Properties

2.1. Dichlorovinylene Carbonate *(2)*

The first representative of the halovinylene carbonates *(2)* was prepared from ethylene carbonate *(6)*[17,18]. Photochlorination of *(6)* according to *Ellingboe* and *Melby*[19] leads *via* compounds *(7)*—*(9)* to tetrachloroethylene carbonate *(10)* (82%), which affords dichlorovinylene carbonate *(2)* (85%) on treatment with Zn(Cu) in ether.

The lacrimatory liquid solidifies to crystals (m.p. 19 °C) below room temperature and can then be stored indefinitely in a refrigerator.



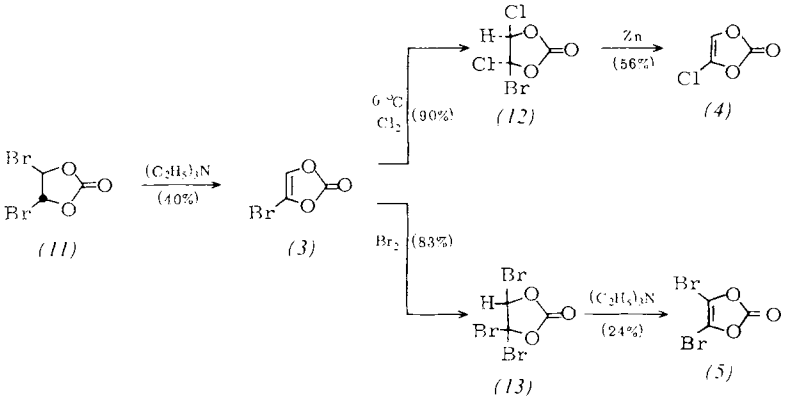
reactions. Even at elevated temperatures (b. p. 143 °C/760 torr) the half-life for cleavage is large compared to the reaction time.

In the presence of triphenylphosphane or trimethyl phosphite, however, *(2)* undergoes spontaneous decomposition with elimination of CO at room temperature[18]. This reaction, whose mechanism has not yet been elucidated, is typical of the halovinylene carbonates *(2)*—*(5)*; it is not observed with the parent compound *(1)* or its dialkyl derivative[13] (X=alkyl). Moreover, it is remarkable that tertiary amines do not induce cleavage.

In how far the purely thermal elimination of CO to form oxalyl chloride can be classified as a cheletropic cleavage has been investigated in a theoretical study[21].

2.2. Monobromovinylene, Monochlorovinylene, and Dibromovinylene Carbonate *(3)*, *(4)*, and *(5)*

Exhaustive free-radical bromination of ethylene carbonate *(6)* in analogy to the chlorination does not lead to a preparatively useful result in the intended sense. Halogen-exchange reactions with compounds *(8)* and *(10)* also prove unsuitable as a



In the liquid state and in dilute aprotic solvents, CO is eliminated to form increasing amounts of oxalyl chloride[18], a fact which has led to erroneous interpretation of UV absorption measurements, especially in the presence of aromatics[20] (see Section 7). The lattice energy apparently contributes to stabilization of the molecule. Experience has shown that small amounts of oxalyl chloride do not interfere in preparative method of preparing the homologous halo derivatives *(3)* and *(5)*. Nor can monochlorovinylene carbonate *(4)* be obtained from *(8)* by elimination of HCl under S_E2 conditions, a result which confirms the *trans* positions of the Cl atoms in *(8)*[22]. In contrast, dibromoethylene carbonate *(11)*, obtained by addition of bromine to *(1)*, eliminates HBr to form *(3)*[23]. Thus *(3)* became the key substance for preparation of *(4)* and *(5)*[24].

Addition of chlorine to *(3)* affords monobromodichloroethylene carbonate *(12)*, which is converted into *(4)* on treatment

[*] The numbering of the ring atoms is based upon that of the 1,3-dioxole system.

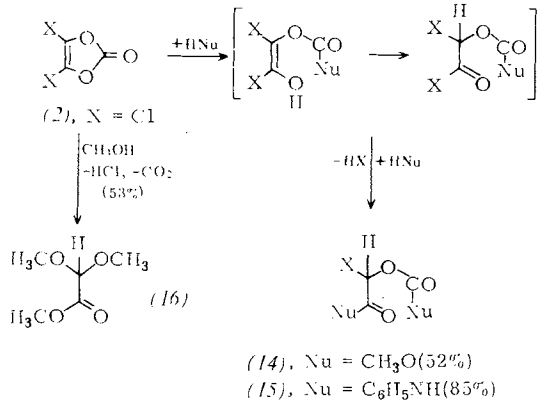
with zinc in ether[24]. Furthermore, *(3)* can be transformed into tribromoethylene carbonate *(13)* which yields dibromovinylene carbonate *(5)* on HBr elimination.

Attempts to prepare diiodovinylene carbonate *(1)*, X = X' = I, by a Finkelstein reaction failed to give any isolable product apart from elemental iodine and CO.

3. Solvolysis Reactions

3.1. Dihalovinylene Carbonates

Methanolysis and aminolysis of *(2)* lead to derivatives of glyoxylic acid. The former reaction initially affords methyl *O*-methoxycarbonylchloroglycolate *(14)*, and the latter the corresponding anilide *(15)*[18].



(2), X = Cl

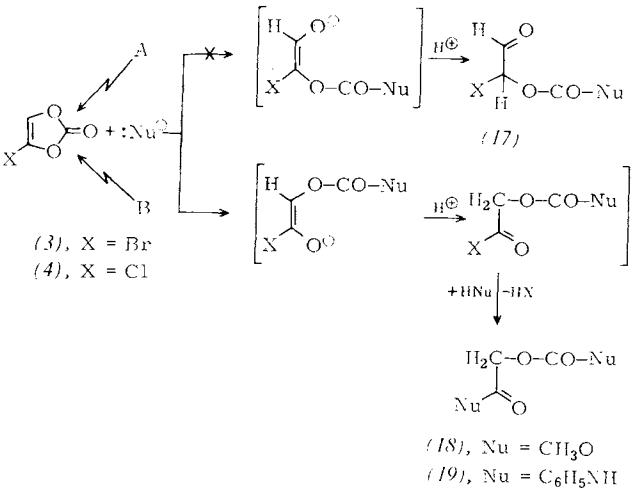
(14), Nu = CH_3O (52%)
(15), Nu = C_6H_5NH (85%)

Methanolysis of *(2)* under reflux or methanolysis of *(14)* under more drastic conditions finally affords the dimethyl acetal *(16)* of methyl glyoxylate.

3.2. Monohalovinylene Carbonates

There are fundamentally two different reaction routes open to solvolysis of the monohalo derivatives *(3)* and *(4)*, depending upon whether the nucleophile initially cleaves bond A or B. Rupture of bond A would lead to a derivative of α-haloglycolaldehyde *(17)*, whereas cleavage of bond B would yield a glycolic acid derivative.

Both alcoholysis and aminolysis give only products arising *via* route B[24]. Treatment with methanol yields methyl *O*-methoxycarbonylglycolate *(18)*, and aniline forms the anilide *(19)*.



(3), X = Br
(4), X = Cl

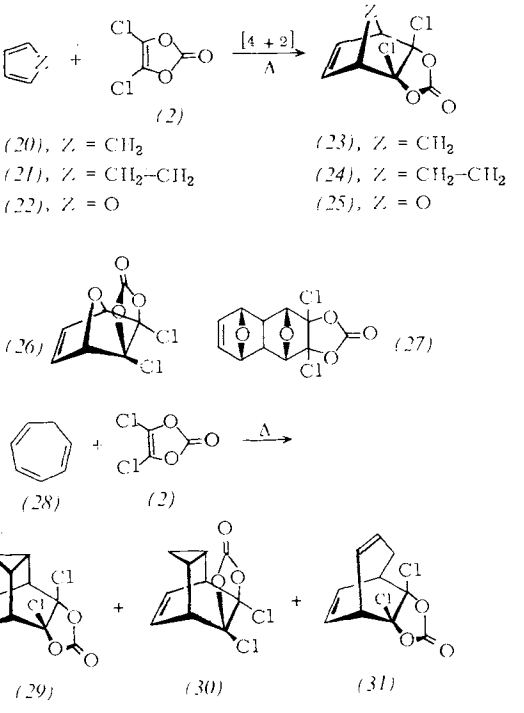
(17)

(18), Nu = CH_3O
(19), Nu = C_6H_5NH

4. [4+2]-Cycloadditions

4.1. Preparative Results

Diels-Alder reaction of *(2)* with a series of 1,3-dienes furnishes [4+2]-cycloadducts, some of which are obtained predominantly in the *exo* form.



(2)

(20), Z = CH_2
(21), Z = CH_2–CH_2
(22), Z = O

(23), Z = CH_2
(24), Z = CH_2–CH_2
(25), Z = O

(26) *(27)*

(28) *(2)*

(29) *(30)* *(31)*

Table 1. Product and reaction data for [4+2]-cycloadditions with *(2)* or *(3)*.

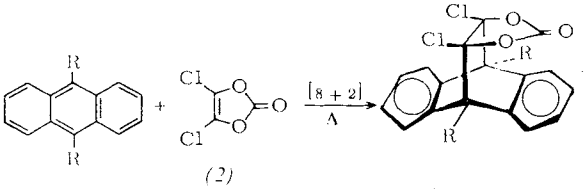
Components	T [°C] [d]	Products, overall yield [%]		Stereoisomers, m.p. [°C]	
(20)+*(2)*	140 [b]	*(23)*, 65–70		only *endo*	148
(21)+*(2)*	140 [b]	*(24)*, 15		only *endo*	216
(22)+*(2)*	180 [a]	*(25)*+*(26)*, 67	(1:2.15)	*(25)*: 181; *(26)*: 118	
(28)+*(2)*	180 [a]	*(29)*+*(30)*+*(31)*, 41	(41.5:25.5:33)	*(31)*: 126	
(32)+*(2)*	140 [b]	*(34)*, 84			218
(33)+*(2)*	140 [b]	*(35)*, 81			221
(37)+*(2)*	140 [b]	*(37)*, 15			76
(20)+*(3)*	189 [c]	*(38)*, 22			76.5

[a] In *o*-dichlorobenzene.
[b] In xylene.
[c] In diethylene glycol diethyl ether.
[d] In a glass autoclave.

While cyclopentadiene *(20)* and 1,3-cyclohexadiene *(21)* give exclusively the corresponding *endo* adducts, *(23)* and *(24)* respectively[25], furan *(22)* is found to give the two stereoisomeric adducts in the ratio *(25)*:*(26)* = 1:2, together with small amounts (1.5%) of a 2:1 adduct *(27)*[26]. In contrast to the adduct of furan and maleic anhydride[27-29] or maleimide[30], attempts at subsequent mutual interconversion of adducts *(25)* and *(26)* at the temperature of formation or above prove unsuccessful, thus justifying the assumption that the *exo* form *(26)* arises on an energetically competitive reaction coordinate with *exo* regioselectivity.

With cycloheptatriene, the three adducts *(29)*–*(31)* are formed. Here too, *exo* preference is observed in contrast to the cycloheptatriene/maleic anhydride adducts[31] which are formed in a ratio of 84:15:1 at 176 C. The structures are analogous to those of *(29)*–*(31)*. Table 1 lists the data for the Diels-Alder adducts formed with *(2)*.

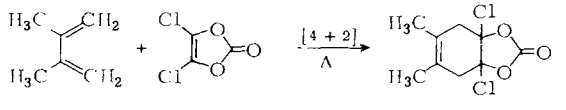
Anthracene *(32)* and its 9,10-dimethyl derivative *(33)* are also suitable as dienes for Diels-Alder reaction with *(2)*[25].



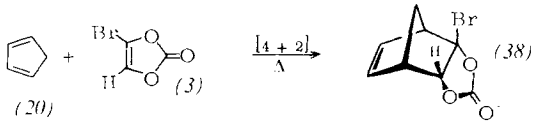
(32), R = H
(33), R = CH_3

(2)

(34), R = H
(35), R = CH_3



(36) *(2)* *(37)*

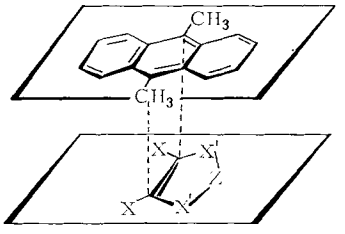


(20) *(3)* *(38)*

Under the usual conditions, *(2)* fails to react with open-chain 1,3-dienes such as butadiene and isoprene. However, a 15% yield of the adduct *(37)* is formed with 2,3-dimethylbutadiene *(36)*[25]. Monobromovinylene carbonate *(3)* likewise affords a Diels-Alder adduct *(38)* (22% yield) with cyclopentadiene[24] (Table 1).

4.2. Kinetic Results[32, 33]

In order to compare the dienophilic activity of the vinylene carbonates *(1)* and *(2)* with those of the corresponding compounds of the maleic acid series—maleic anhydride *(39)* and dichloromaleic anhydride *(40)*—towards 9,10-dimethylanthracene *(33)*, the activation parameters of the reactions were measured (or taken from the literature[34]) (see Table 2).



(33)

(1), *(2)*, *(39)* *(40)*

Table 2. Kinetic data for the reactions of *(1)*, *(2)*, and *(40)* with the diene *(33)*, and values obtained by *Sauer et al.* [34] for *(39)*/*(33)*. k_2 refers to 130 C.

Dienophile				$10^4\,k_2$	E_A	$\Delta H^{\neq}$	$\Delta S^{\neq}$	$(k_2)_{rel.}$
	X	X'	Z	[l mol^{-1} s^{-1}]	[kcal mol^{-1}]	[kcal mol^{-1}]	[cal mol^{-1} K^{-1}]	
(39)	H	CO	O	14100	10.9	10.2	−33	10071
(40)	Cl	CO	O	145	13.1 ± 0.4	12.4 ± 0.4	−37	104
(2)	Cl	O	CO	8.7	17.2 ± 0.3	16.5 ± 0.3	−32	6.2
(1)	H	O	CO	1.4	22 ± 1.3	21.5 ± 1.3	−23	1

In the case of the maleic acid derivatives *(39)* and *(40)*, chlorine substitution at the double bond of the dienophile raises the activation barrier of the reaction with *(33)*, while in the carbonate series reaction with the dichloro compound *(2)* proceeds slightly more readily than with the parent compound *(1)*. The activation entropies found for reactions with *(39)*, *(40)*, and *(2)* are normal, in agreement with literature values[35], while the reaction with *(1)* displays a surprisingly low value[36].

Assuming that the magnitude of the frontier orbital interaction between the reactants at the start of reaction plays a dominant role in controlling the height of the activation barriers[37, 38] enables us to reach a qualitative understanding of the differing effects of chlorine substitution in the two classes of compounds.

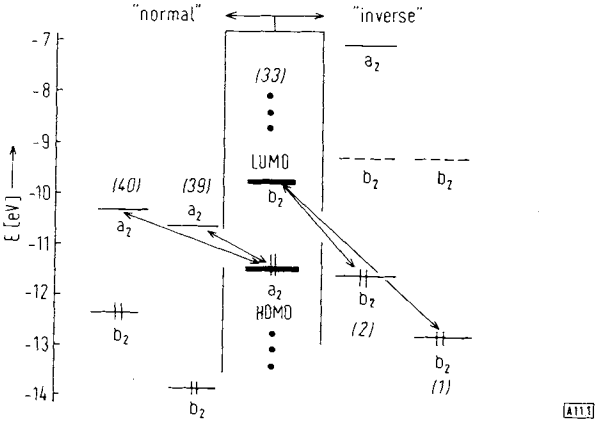


Fig. 1. Comparison of $[4\pi_s + 2\pi_s]$-cycloadditions with "normal" and with "inverse" electron demands. The plot shows the EHT MO energies [39] calculated for compounds *(1)*, *(2)*, *(33)*, *(39)*, and *(40)*. See text for details.

The calculated[39] orbital energies of the reactants are plotted in Figure 1. The symmetry-correct interactions of the HOMO of *(33)* with the pertinent LUMO of *(39)* and *(40)*, which lead to an energy-lowering splitting along the reaction coordinate, show that owing to the greater energy difference in the case of *(40)* the activation energy of this reaction will be higher than in the case of *(39)*.

Since both dienophiles are "electron deficient", *i.e.* possess high ionization energies, whereas the diene *(33)* is "electron rich", these reactions are classified as "normal" Diels-Alder reactions[40]. A different situation is encountered with compounds *(1)* and *(2)*. Here a symmetry-correct interaction can only occur between the respective HOMO of *(1)* and *(2)* and the LUMO of *(33)*, in such a manner that a higher activation barrier is to be expected in the reaction with *(1)* because of the greater difference in energy. Owing to the direction of electronic polarization, these reactions are said to belong to Diels-Alder reactions having "inverse" electron demands[41,35][*].

Application of second order perturbation theory[38,42] also permits rationalization of the regioselectivity of the [4+2]-cycloaddition of *(2)* to furan and estimation of the *exo* preference. For this purpose the EHT MO energies[39] and the corresponding LCAO MO coefficients are shown in Figure 2 for the energy levels of furan and the cyclophile *(2)* which are relevant in a zero-order approximation.

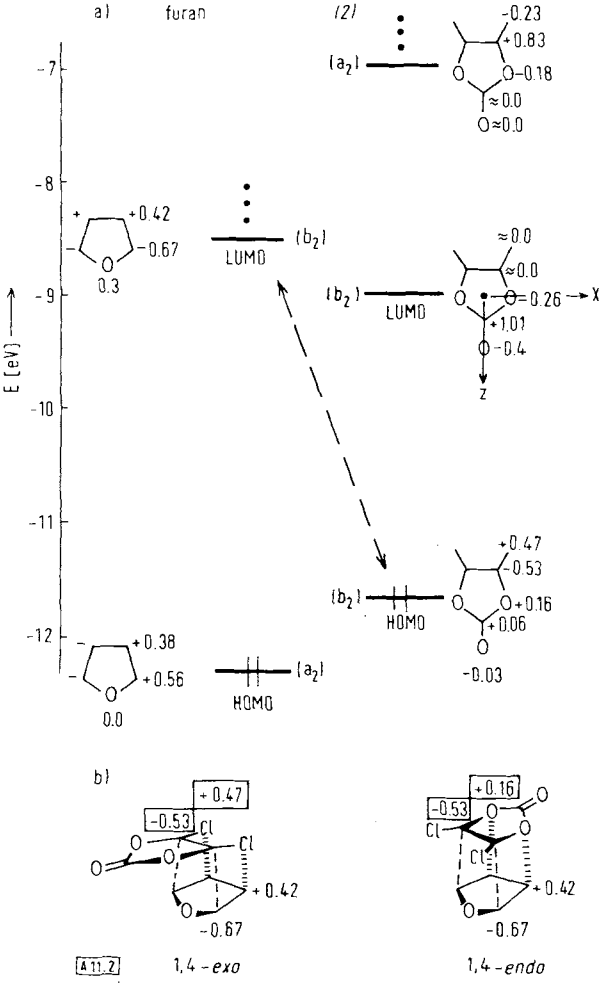


Fig. 2. Explanation of the regioselectivity of the [4+2]-cycloaddition of dichlorovinylene carbonate *(2)* to furan. a) EHT MO energies [39] and LCAO MO coefficients. b) Calculation of the stabilization component ΔE for 1,4-*exo* and 1,4-*endo* addition. For details see text.

$\Delta E_{exo} \approx 2[-0.53][-0.67]+[0.47][0.42])^2/(E_{HOMO(2)}-E_{LUMO(furan)})$

$\Delta E_{endo} \approx 2([-0.53][-0.67]+[0.16][0.42])^2/(E_{HOMO(2)}-E_{LUMO(furan)})$

[*] Experimental ionization energies for *(1)*, 10.3, and for *(2)*, 9.92 eV. *H. Bock* and *K. Wittel*, personal communication.

If it is assumed, in keeping with second-order perturbation theory for cycloaddition with simultaneous bond formation between two or more reaction centers of the reactants[43], that the route-determining stabilization component ΔE of the π-electron energy is primarily proportional to the square of the sum of the coefficient products taken over the interacting centers of the reactants, and inversely proportional to the energy gap between the levels considered [HOMO*(2)* and LUMO(furan)], then the *exo* preference of the reactants can be explained as follows:

The secondary interaction of the Cl atoms of *(2)* with positions 3 and 4 of furan in the *exo* arrangement is greater (+0.47) than the secondary interaction with the oxygen atoms (+0.16) in the *endo* orientation.

It thus also becomes understandable why the parent compound *(1)* adds mainly *endo*-selectively[2-4,7,8] in the thermal [4+2]-cycloadditions known so far.

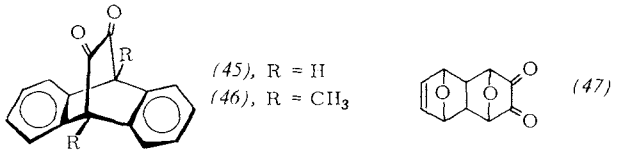
Considerations of this kind are obviously very crude: they can claim no more than to indicate general trends. Nevertheless, regioselectivities can be articulated more precisely in this manner than in terms of the stereochemical rules derived empirically[44].

5. α-Diketones and Simple Derivatives

Hydrolysis of the [4+2]-cycloadducts *(23)*—*(27)*, *(29)*—*(31)*, *(34)*, and *(35)* afford bridged α-diketones, some of which were hitherto unknown. The initial products are condensed hydrate forms from which the α-diketones *(41)*—*(47)*[25,26] can be obtained pure by sublimation (Table 3).

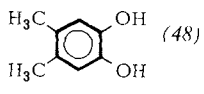


(41) Z = CH_2 *(41a)*
(42) Z = CH_2-CH_2 *(42a)*
(43) Z = O *(43a)*
(44) Z = ▷ *(44a)*

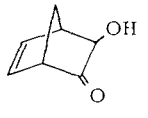


(45), R = H
(46), R = CH_3

(47)



(48)



(49)

Hydrolysis of compound *(37)* expectedly yields 4,5-dimethylpyrocatechol *(48)*, while adducts with monohalovinylene carbonates, *e.g. (38)*, lead to 3-hydroxy-5-norbornen-2-one *(49)* (Table 3). No spectroscopic evidence is obtained for the presence of the enediol form in this substance. The monoketals are readily formed by methanolysis of the cycloadducts in the presence of hydrogen carbonate. The α-diketones *(41)*, *(42)*, and *(44)*—*(46)* are yellow to orange, and the diketones *(43)* and *(47)* are red. This deepening of color is apparently due to interaction between the oxygen p orbital, which is symmetrical with respect to the molecular plane, and the

ψ_1 orbital of the "diene" grouping formed from the two keto groups positioned α to each other. Owing to the ensuing splitting, the energy gap to the lowest unoccupied π* level is reduced.

ketones[56–60]. On irradiation, the ketals *(41a)* and *(43a)* are in photochemical equilibrium with the four-membered cyclic ketals *(41b)* and *(43b)* respectively. The reacting excited state is most probably a singlet. Nevertheless, the reaction

Table 3. α-Diketones and their monodimethyl acetals prepared by hydrolysis and methanolysis, respectively, of the adducts *(23)*—*(27)*, *(29)*—*(31)*, *(34)*, and *(35)*.

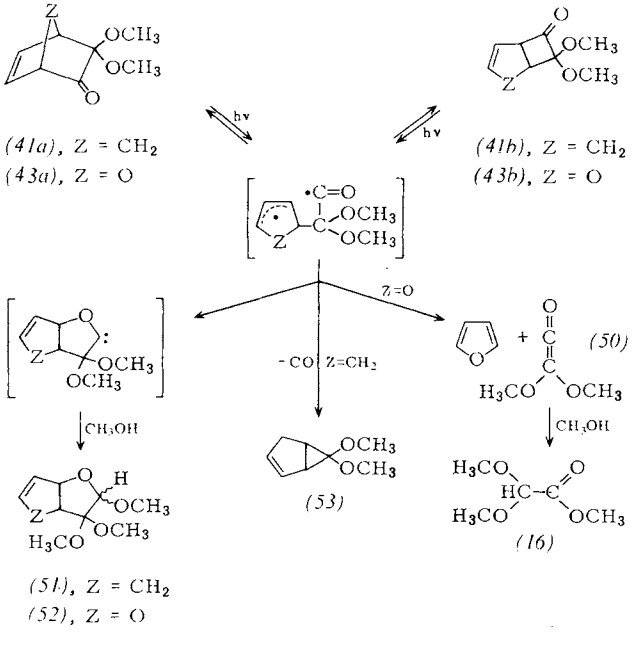
Adduct(s)	Diketone	M.p. [°C]	Yield [%]	Ref.	Ketal	Yield [%]	B.p. [°C/torr]
(23)	*(41)*	43 [49]	61	[25]	*(41a)* [25]	83	98/10 [a]
(24)	*(42)*	81	78	[25, 45]			
(25), *(26)*	*(43)*	66	56	[26]	*(43a)* [26]	80	106–107/10
(29), *(30)*, *(31)*	*(44)*	102	83	[26]	*(44a)* [26]	60	66/0.1
(34)	*(45)*	198	78	[25, 46, 47]			
(35)	*(46)*	188	82	[25]			
(27)	*(47)*	185	47				
(37)	*(48)*	88	85	[48]			
(38)	*(49)*		24				

[a] $n_D^{20} = 1.4770$.

5.1. Photolytic and Thermolytic Studies

The α-diketones *(41)*—*(46)* and the monoketals *(41a)*, *(43a)*, and *(44a)* are formally Diels-Alder adducts of the parent dienes with the hitherto unknown "bisketene" C_2O_2, unsuccessfully sought by *Staudinger*[50], and its monoketal dimethoxyketene *(50)*, respectively. Since both these cyclophiles—provided they exist at all—would be antarafacial reactants, preparation of the above cycloadducts by $[4\pi_s + 2\pi_s]$ Diels-Alder addition is impossible. Once the cycloadducts had become available by the above route, however, it seemed obvious to attempt a preparation of the unknown cyclophiles C_2O_2 and *(50)* by $[4\pi_s + 2\pi_a]$ cycloreversion of the adducts, which should possess a favorable reaction coordinate when performed photochemically. Photolysis of the diketones *(41)*—*(46)* leads almost completely to the dienes and carbon monoxide. No experimental evidence is obtained for the transient occurrence of C_2O_2[51–54].

Photolysis of the monoketals *(41a)*[55] and *(43a)*[26] follows a fairly uniform mechanism resembling that of β,γ-unsaturated



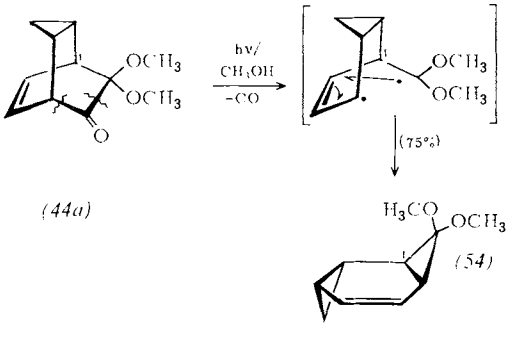
does not involve a concerted sigmatropic $[1,3]_s$ shift; instead, initial formation of a diradical intermediate capable of a variety of further reactions has to be assumed on the basis of temperature dependence.

Isomerization of the diradical intermediate to a cyclic oxycarbene ("oxacarbene") and subsequent addition of methanol leads to the stereoisomers of compounds *(51)* and *(52)*, whose stereochemistry could be established by NMR spectroscopy with aid of paramagnetic shift reagents[61, 26].

Decarbonylation occurs only for $Z = CH_2$ to form the dimethyl ketal of bicyclo[3.1.0]hex-2-en-6-one *(53)*.

When Z = O, the diradical decomposes to furan and dimethoxyketene *(50)* which can be trapped as the dimethyl acetal of the glyoxylic ester *(16)* with methanol[26]. This cleavage, which was formerly observed on photolysis of dehydronorcamphor[56], does not occur with *(41a)* ($Z = CH_2$), thus also confirming the intermediacy of the diradical whose substituent effects depending upon Z are manifested in the varying cleavage pattern.

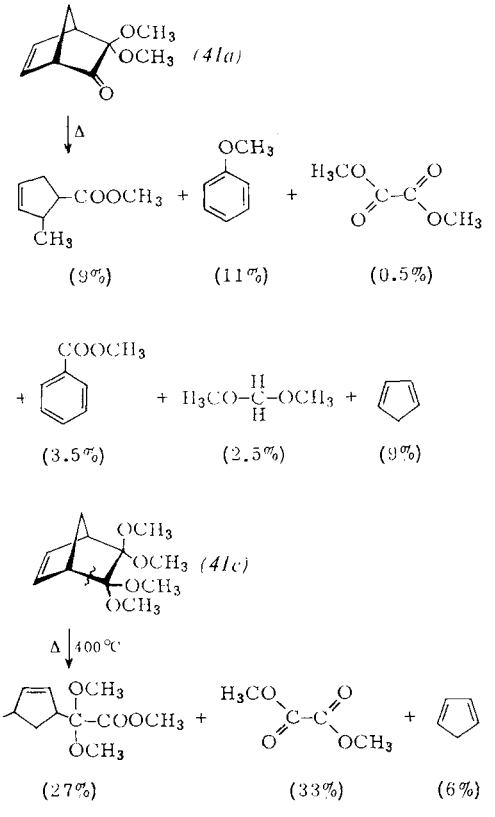
Photolysis of *(44a)* with decarbonylation proceeds in highly uniform manner, and has been utilized in an elegant synthetic route to the σ-bishomobenzene series, *e.g.* to *(54)*[26]. This finding can likewise be rationalized by assuming an intermediate diradical.



The *trans* conformation of the two cyclopropane rings follows compellingly from the stereochemistry of the original monoketal *(44a)* and is confirmed by ^{1}H-NMR spectroscopy[62].

These results would indicate that—despite participation of singlet states—the fragmentation reactions proceed in a step-

wise manner, *i. e.* the coordinates of the concerted $[4\pi_s+2\pi_a]$ cycloreversion apparently lie at higher energy than would correspond to the energy of the light quantum of the incident radiation. Since the cyclophiles considered are antarafacial components even higher energies are to be expected for $[4\pi_s+2\pi_s]$ cycloreversion. It is therefore not surprising that thermolysis is by no means homogeneous but yields a wealth of fragments whose genetic sequences have not yet been elucidated[63]. The results of thermolysis of compounds *(41a)* and *(41c)* serve as illustrative examples.

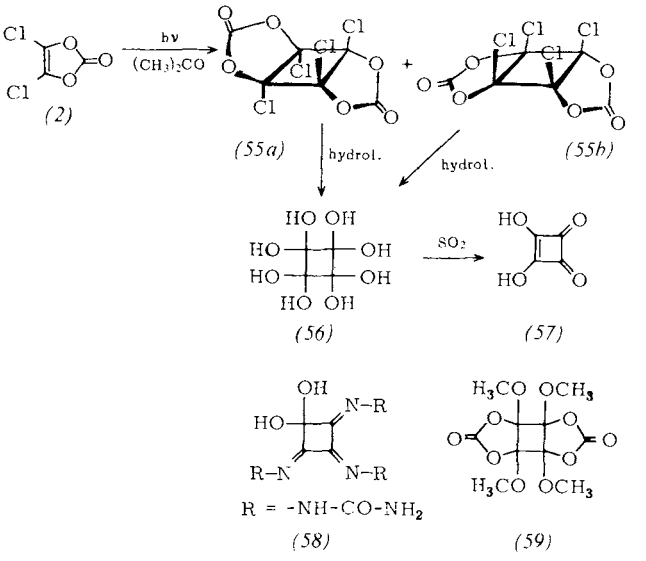


The bis(dimethyl ketal) *(41c)* of norbornenedione *(41)* can be formally regarded as the Diels-Alder adduct of tetramethoxyethylene to cyclopentadiene, although it cannot be prepared from the components[64]. In this case too, the $[4\pi_s+2\pi_s]$ cycloreversion coordinate appears to be energetically very high. Hence thermolysis of *(41c)* only affords compounds to be viewed as stabilization products of intermediate radical fragments[65]. These adducts *(41a)* and *(41c)*, which are obtainable *via* cycloaddition of 1,3-dienes to dichlorovinylene carbonate *(2)*, can therefore be termed "pseudo-Diels-Alder adducts".

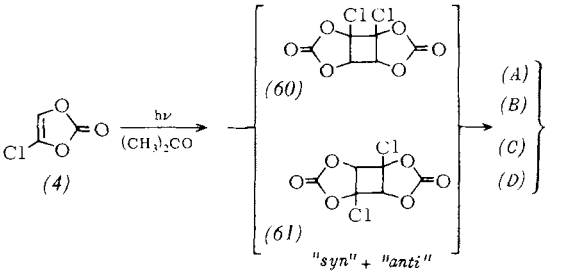
6. [2+2]-Cycloadditions

6.1. Photochemical Cyclodimerization of Di- and Monochlorovinylene Carbonate *(2)* and *(4)*

Dichlorovinylene carbonate *(2)* can be dimerized to form two stereoisomeric cyclobutane derivatives *(55a)* and *(55b)*[66] by irradiation in acetone; both isomers yield octahydrocyclobutane *(56)* which was obtained by *West, Niu,* and *Ito*[67] on oxidation of squaric acid *(57)* with nitric acid. Squaric acid is formed from *(56)* by the action of SO_2. As with other hydrated forms of cyclooligomeric carbon monoxide $(CO)_n$, dehydration always modifies the molecule[68]. However, *(55a)* which is more readily obtained in crystalline form, can be converted into an orange cyclobutanetetrone tris(semicarbazone) monohydrate *(58)* by treatment with semicarbazide hydrogen chloride.



The chlorine atoms of the isomers *(55)* undergo extremely ready nucleophilic replacement prior to solvolytic opening of the carbonate ring. Dissolution in, *e.g.*, methanol leads very rapidly to a homogeneous tetramethoxy compound *(59)* of unknown stereochemistry; no intermediates can be detected by gas chromatography.

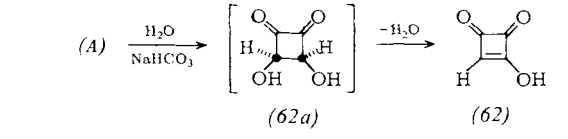


Irradiation of 1 : 1 mixtures of monochlorovinylene carbonate *(4)* and acetone with the aid of a high-pressure mercury lamp leads to the formation of four stereoisomeric C_4-cyclodimers *(A)*—*(D)*, one of which [*(A)*] is relatively insoluble and precipitates during irradiation[24]. The stereochemical details have yet to be elucidated.

Table 4. Physical properties of the C_4-dimers of monochlorovinylene carbonate *(4)*.

	(A)	*(B)*	*(C)*	*(D)*
M.p. [°C]	189	191	109	179–80
IR [a]:	1815	1840	1860	1820
$\nu_{C=O}$	1845			1840
^{1}H-NMR [b]: τ [ppm]	6.13 (s)	6.10 (s)	5.91 (s)	6.09 (s)

[a] In KBr.
[b] In [D_6]-acetone.



Hydrolysis of the easily obtainable dimer *(A)* yields the hydroxycyclobutenedione *(62)*[24, 117, 118].

The formation of *(62)* from dimer *(A)* by hydrolysis allows conclusions to be drawn regarding its stereochemistry: The 1,2 arrangement of the CO groups in *(62)* is obviously due to the vicinal arrangement of the Cl atoms in *(A)*, and the ready elimination of water from the intermediate dihydrosquaric acid *(62a)* suggests a *syn* configuration of the carbonate rings with regard to the four-membered ring.

Recently, *Cole et al.*[119] have isolated *(62)* as baceterial toxin from *Fusarium moniliforme* and *Gibberella fujikuroi*, and elucidated the structure of its potassium salt by X-ray analysis[120]. The compound, which has been designated "moniliformin", exhibits biocidal properties.

6.2. Cyclodimerization of Dichlorovinylene Carbonate *(2)* with Olefins

Preparation of cyclobutane derivatives from simple olefins and *(2)* by sensitized photocycloaddition proceeds readily and gives good to very good yields[69, 70]. Experience has shown acetophenone to be a highly effective sensitizer; diethyl ether, dioxane, and diethylene glycol diethyl ether have proved their value as solvents.

As the simplest open-chain olefin, ethylene reacts with *(2)* to give the cyclobutane derivative *(63)*[17] without side-products at room temperature. Cyclic olefins having $n>3$ afford adducts having typical linkage patterns. For instance, cyclohexene *(65)* ($n=4$) gives a *trans* adduct *(71)* as well as the *anti* and *syn* adducts *(70)* and *(68)*. Formation of *(71)* evidences a multi-step reaction course. The stereochemistry was established by ^{1}H-NMR studies[70] (Table 5).

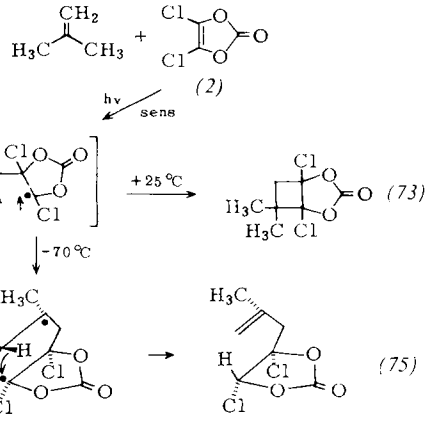
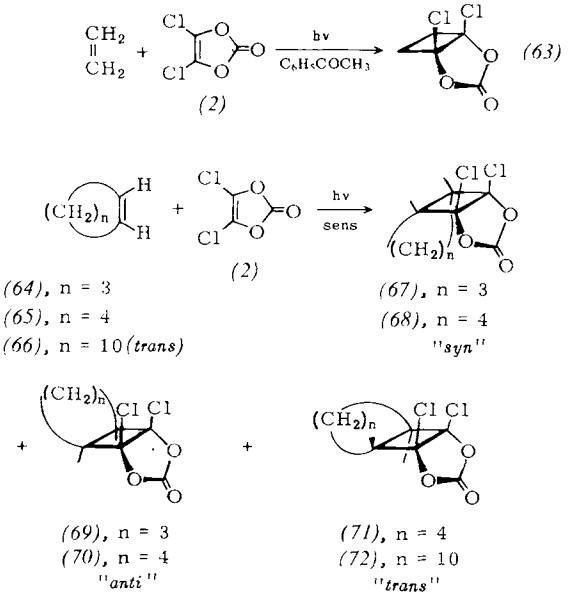


Table 5. Cyclobutane derivatives from *(2)* and olefins. Sensitizer: acetophenone or acetone; solvent: dioxane; light source: HPK 125 Philips UV lamp, Pyrex filter.

Olefin	Adduct	Yield [%] [a]	Isomeric comp.	M.p. [°C]	Ref.
Ethylene	*(63)*			54	[17, 70]
Isobutylene	*(73)*				[71]
Cyclopentene *(64)*	*(67)*	95	49	99.5	[70]
	(69)		51	58.5	
Cyclohexene *(65)*	*(68)*		23.2	59	[70]
	(70)	95	40.5	74	
	(71)		36.3	43	
trans-Cyclododecene *(66)*	*(72)*	41		97	[69]

[a] The yield is based on the amount of *(2)* in the starting materials (2.5 mol/l solvent); olefin concentration 2.5 mol/l.



Proof of a typical reaction sequence with participation of a diradical intermediate was obtained with *(2)* and isobutylene as reactants[71]. At room temperature, only the cyclobutane derivative *(73)* is obtained. However, at −70 °C compound *(75)* also arises. Its formation doubtless involves intramolecular H abstraction from the diradical *(74)* which appears to be subject to hindrance at low temperature.

6.3. The Question of Photosensitization in Cycloadditions of Dichlorovinylene Carbonate *(2)* to Olefins

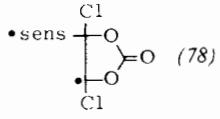
Above 200 nm the UV spectrum of pure *(2)* exhibits no bands other than the end absorption. Spurious bands in the 300—360 nm[120] range are due to oxalylchloride present as impurity[70]. If the excellent sensitizing effect of acetophenone ($E_T=74$ kcal/mol)[72] or acetone ($E_T=79.5$—82 kcal/mol)[73], in cycloadditions of *(2)* with olefins is interpreted as being due to triplet energy transfer, then the energy E_T of the lowest triplet level of *(2)* would have to lie <74 kcal/mol above the ground state.

PPP calculations[74] as well as quantum yield measurements on sensitized cycloaddition reactions with application of sensitizers of decreasing triplet energy[75] reveals that the lowest triplet term of *(2)* is 68—70 kcal/mol above the ground state.

Moreover, the quenching constant for the Norrish Type II cleavage of butyrophenone by *(2)* is found to be $k_q = 5.6 \times 10^8\ l\ m^{-1}\ s^{-1}$[76]. These results suggest that a triplet-energy transfer from the above sensitizers to *(2)* is very likely.

The photoreaction of *(2)* with furan to give *(90)*, *(92)*, and *(94)* (see Section 6.5) again belongs to the class of sensitized photocycloadditions, *i.e.* in the absence of sensitizer, *e.g.* acetophenone, no reaction occurs.

The photopinacolization of acetophenone on irradiation of its ethereal solution, which was observed by *Ciamician* and *Silber*[78], is suppressed only slightly by furan, but strongly in the presence of furan and *(2)*, in favor of photoadduct formation [*(90)*, *(92)*, *(94)*][26].



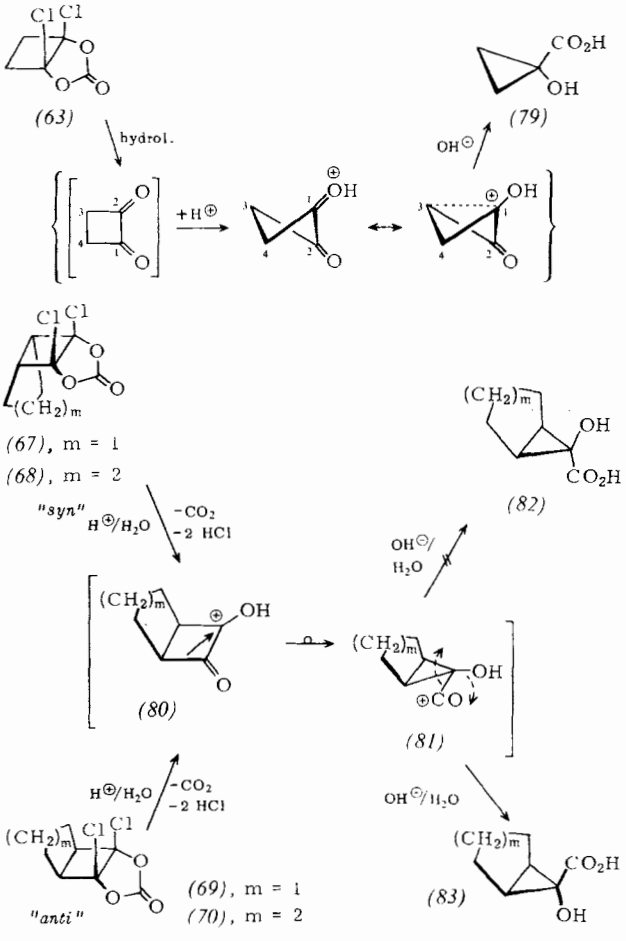
(78)

Although the intermediate existence of a 1,4-biradical such as *(78)* cannot be completely ruled out on the basis of these results, we again favor triplet-energy transfer from ^{3}Sens* to *(2)*.

The same applies to the photosensitized dimerization of *(2)* to *(55a)* and *(55b)* and of *(4)* to *(60)* and *(61)*.

6.4. Synthesis of α-Hydroxycyclopropanecarboxylic Acids

Compounds *(63)* and *(67)—(72)* possessing potential α-diketo functions should transform into α-diketones of the cyclobutane series or their hydrate forms on hydrolysis. It frequently proves possible to briefly observe the typical UV spectra[79,85] of 1,2-cyclobutadiones[80–85] which have meanwhile become accessible by another route. They can also be trapped by phenyl hydrazine, but resist isolation[86]. Instead, they rearrange to α-hydroxycyclopropanecarboxylic acids, *e.g.* *(63)* affords *(79)*, in protic solvents[17,87].

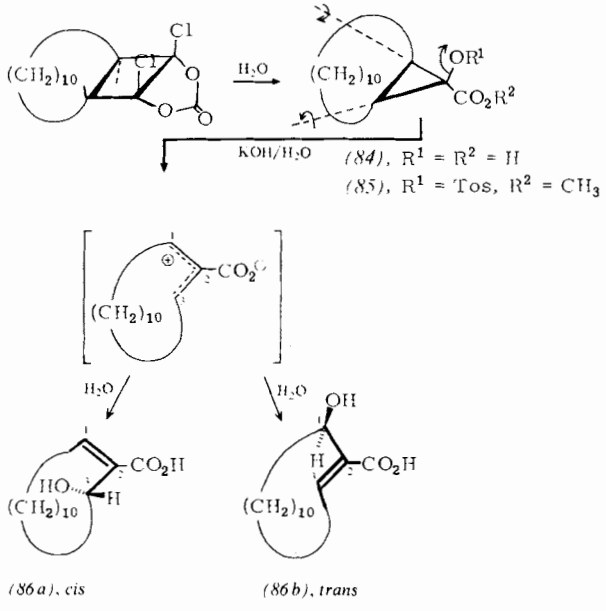


This reaction, which renders the α-hydroxycyclopropanecarboxylic acids readily accessible (Table 6), displays an interesting stereoselection. The stereoisomeric cycloadducts *(67)* and *(69)* should afford the two likewise stereoisomeric 1-hydroxybicyclo[3.1.0]hexanecarboxylic acids *(82)*, $m=1$, and *(83)*, $m=1$, respectively, since the carbenium ion resulting on opening of the cyclic cation *(80)* can escape both "upwards" and "downwards". The same applies to *(68)* and *(70)*. However, isomers of type *(83)* are formed exclusively without any detectable trace of the isomeric compounds *(82)*.

Table 6. α-Hydroxycyclopropane derivatives.

Cpd.	M. p. [°C]	Yield [%]	Ref.
(79)	108	95	[17, 85, 89]
(83), $m=1$	106	85	[86]
(83), $m=2$	129—130	81	[86]
(84)	161	73	[69]

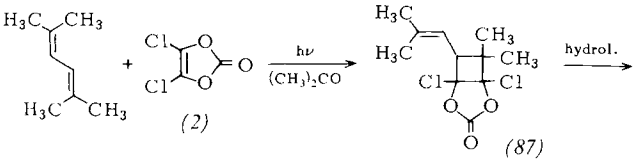
Since similar results are obtained on protonation of bicyclo[*m*.2.0]alkane-(*m*+3), (+4)-diones, which have meanwhile become available[87,88], formulation *via* the intermediates of type *(80)* and *(81)* is justified. The reason behind this stereoselectivity has not yet been elucidated.



Solvolysis of the tosylates of *(83)*, $m=1$ and $m=2$, and of *(84)* proceeds *via* a disrotatory opening of the cyclopropane ring with ring expansion to give β-hydroxycycloalkenecarboxylic acids. Thus equimolar amounts of the β-hydroxycyclotridecenecarboxylic acids *(86a)* and *(86b)* are obtained from *(84)* or *(85)*[69].

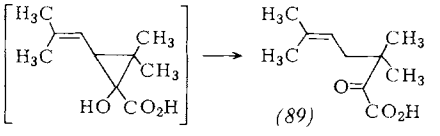
6.5. Dienes as Cycloaddition Components

The photochemical cycloaddition of *(2)* to 1,3-dienes proceeds with a widely varying degree of success. 2,5-Dimethyl-2,4-hexadiene affords two stereoisomeric adducts *(87)* in only moderate yield[71]. The reason most probably lies in the excellent quenching properties of the dienes towards photoexcited ketones, which strongly reduce the sensitizing action.

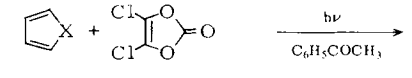


(2) *(87)*

2 isomers

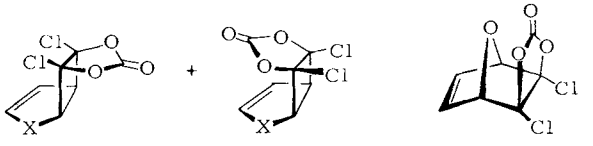


(88) *(89)*



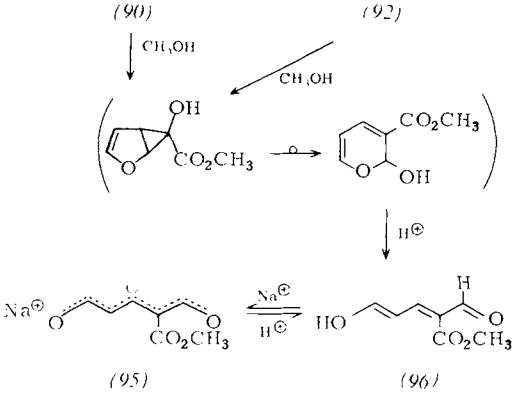
(2)

X = O, S



(90), X = O *(92)*, X = O *(94)*
(91), X = S *(93)*, X = S

However, α-hydroxychrysanthemumic acid *(88)* cannot be isolated on hydrolysis: the tautomeric keto form *(89)* appears very readily. Experience shows that the α-hydroxycyclopropanecarboxylic acids having a double bond conjugated with the three-membered ring yield the tautomeric keto forms very rapidly.



(95) *(96)*

The yields obtainable from heterocyclic dienes such as furan[26] and thiophene[26,90] again vary widely. While furan affords the isomers *(90)*, *(92)*, and *(94)* in the ratio 16:25:9 (60% overall yield), thiophene furnishes only 9.5% of the cyclobutane derivatives *(91)* and *(93)*. A photochemical *exo*-[4+2]-cycloadduct analogous to the furan derivative *(94)* is not observed in the case of thiophene[91].

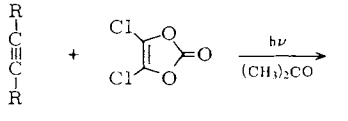
Methanolysis of *(90)* and *(92)* in the presence of sodium carbonate proceeds *via* a series of consecutive reactions to form the sodium salt of the dienologous carboxylic acid *(96)*[26], a derivative of glutaconic dialdehyde. The sodium salt *(95)* is deep red in aqueous solution, whereas the dienologous acid *(96)* is yellow. They co-exist in a pH-dependent reversible equilibrium: the system can therefore be employed as an indicator.

The substance reduces Fehling's solution and gives violet colorations typical for β- and δ-dicarbonyl compounds with Fe^{3+}.

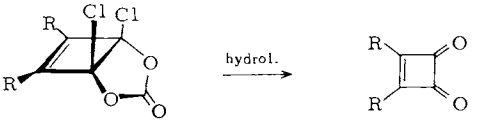
6.6. Alkynes as Cycloaddition Components

Acetylene[92] and 2-butyne[93] are suitable for sensitized [2+2]-cycloaddition to *(2)*. In solution at room temperature, *(97)* is formed in only poor yield from acetylene and *(2)*. The cyclobutenedione *(98)* has nevertheless been prepared in this way by subsequent hydrolysis of *(97)*.

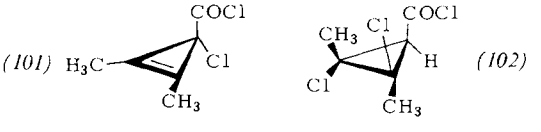
The photoreaction of *(2)* with 2-butyne proceeds less clearly. The product *(99)* is accompanied by *(101)* and *(102)*. However, product analysis and the temperature and solvent dependence of the reaction do provide an insight into the pertinent cycloaddition mechanism. Both *(99)* and *(101)* arise from a common photochemically generated intermediate *(103)* which must possess a strongly polar structure since it is stabilized only in polar solvents such as acetone or acetonitrile. It eliminates CO_2 to form the cyclopropene derivative *(101)*. Intermediate *(103)* is essentially a 1,4-diradical *(103a)* which collapses to a 1,4-dipole *(103b)* in an intramolecular redox reaction; ring closure to the cyclopropene system occurs with loss of CO_2.



R = H, CH_3 *(2)*

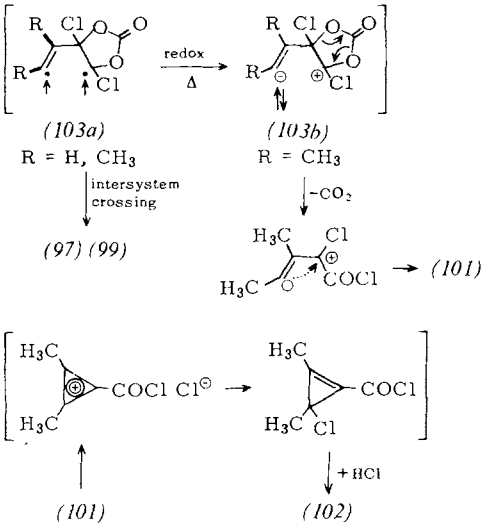


(97), R = H *(98)*, R = H
(99), R = CH_3 *(100)*, R = CH_3



An activation barrier must exist between *(103a)* and *(103b)* since only *(99)* is formed at low temperatures. *trans*-2,3-Dichloro-2,3-dimethylcyclopropanecarbonyl chloride *(102)* arises from *(101)* in a dark reaction by the action of hydrogen chloride formed as side-product in the photoreaction. Formation of *(102)* can be rationalized as involving an intermediate

cyclopropenylium ion, and can be accomplished with pure *(101)* and HCl. Hydrolysis of *(99)* yields dimethylcyclobutenedione *(100)* which is identical with the product obtained by *Blomquist* and *Vierling via* an alternative route[94].



In general it may be said that the photocycloadditions of *(22)* to alkynes at room temperature give much lower yields and are usually less selctive than to alkenes. At low temperatures (−30 to −40 °C), however, the adducts *(97)* and *(99)* are obtained exclusively as homogeneous products. Hence the reaction can compete effectively with other more complicated procedures[95].

7. Photochemical Additions to Benzene and Naphthalene

The classical photochemical cycloaddition of maleic anhydride to benzene provided the impetus for an understanding of the use of simple aromatic compounds as cycloaddition partners[96–99].

It was deduced from a large number of studies that the actual reactive species in the case of maleic anhydride and benzene is a charge transfer complex of the reactants[100] which is subject to nucleophilic attack by a further molecule of maleic anhydride in the course of the reaction, leading to stereospecific formation of the known 2:1 adduct[77].

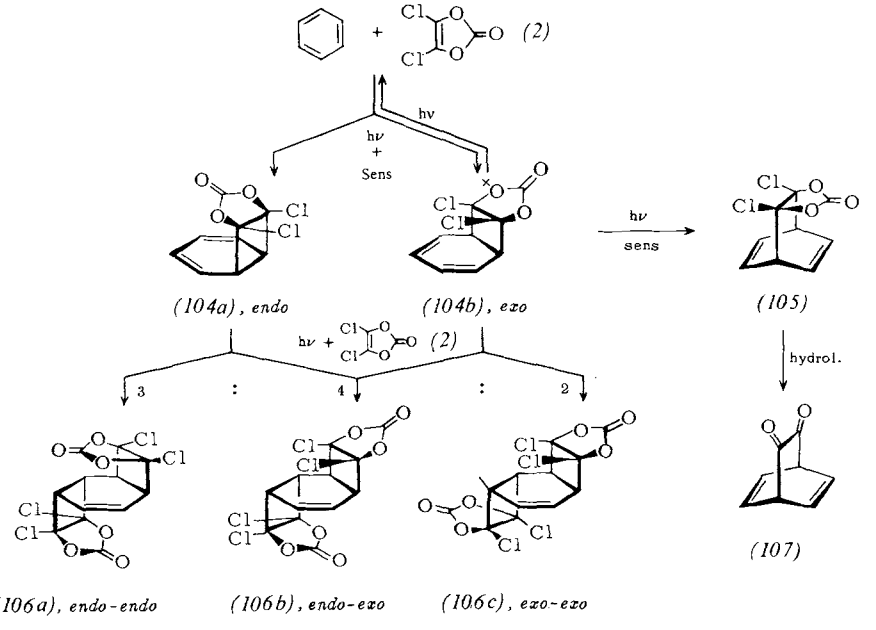
Meanwhile, further experimental results have shown how olefins and dienes undergo photochemical cycloaddition to benzene[101–103] and naphthalene, and *Bryce-Smith* has collected a number of fundamental cases of symmetry-controlled cycloadditions to benzene under photochemical conditions[101, 109].

Accepting this concept, then a concerted 1,2- or 1,4-cycloaddition with retention of configuration at the linkage sites is "allowed" only if the added molecule reacts from the S_1 state with S_0 benzene or if benzene reacts from the $S_2(^1B_{1u})$ state with the S_0 olefin. In contrast, reaction of $S_1(^1B_{2u})$ benzene with the S_0 olefin is symmetry-forbidden so long as no charge transfer complexes or exiplexes of the reactants are involved[101, 103].

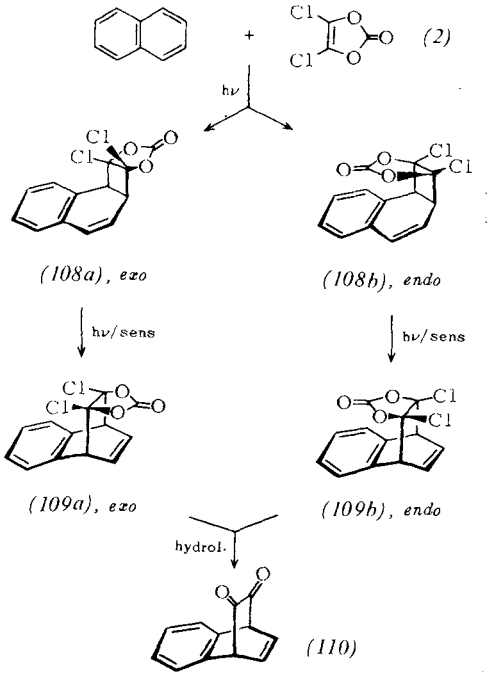
The study of the photochemical addition of *(2)* to benzene and naphthalene commanded not only preparative interest, as repeatedly mentioned, but mechanistic interest too, because, in spite of claims to the contrary[20, 110], no charge transfer complex between the reactants could be detected[70].

On photoaddition of *(2)* to benzene[70, 20, 110–113] with acetophenone or 2-butanone as sensitizer, only the 1,2-cycloadduct *(104b)* can initially be isolated from the mixture after brief irradiation since it crystallizes from the reaction mixture[111, 112, 70].

On further irradiation the concentration of *(104b)* steadily decreases in favor of the 1,4-cycloadduct *(105)* and the two stereoisomeric 2:1 adducts *(106b)* and *(106c)*. Since the 2:1 adduct *(106a)* can also be isolated, it has to be assumed that the *endo*-isomeric 1,2-cycloadduct *(104a)* is formed but presumably undergoes very fast reaction and thus escapes detection owing to an insufficient steady-state concentration. In the presence of the sensitizers employed, the isolated *exo* 1,2-adduct is partly cleaved to the starting compounds and partly rearranges to the 1,4-adduct *(105)*. The above time dependence of the concentration of *(104b)* becomes understandable in the light of these observations.



However, the structure and stereochemistry of the products have been established. The 1,4-adduct *(105)* is formally the Diels-Alder adduct of *(2)* to benzene; the adduct cannot be obtained by a thermal route. This compound proved to be a suitable starting material for the preparation of the hitherto unknown bicyclo[2.2.2]octa-5,7-dien-2,3-dione *(107)*[112] which, unlike the non-isolable homologous norbornadien-7-one[113], is fairly stable thermally. However, *(107)* undergoes very ready photochemical decomposition to benzene and carbon monoxide.



On irradiation of naphthalene/*(2)* solutions[115] under conditions ensuring that only naphthalene can absorb light, the primary products, as in the case of benzene, are the isomeric 1,2-adducts *(108a)* and *(108b)*, and after prolonged irradiation the 1,4-adducts *(109a)* and *(109b)*. All compounds have been isolated and their stereochemistry established by ^{1}H-NMR spectroscopy with the aid of lanthanoid shift reagents[61].

On selective irradiation in the longest wavelength absorption band of naphthalene the same reaction course is operative as is observed on irradiation with the unfiltered light of a high pressure mercury lamp. The initial products are the 1,2-cycloadducts *(108)* which then disappear in favor of the 1,4-cycloadducts *(109)*. Preparative isolation of the 1,2-adducts *(108)* from the reaction mixture therefore proved to be more problematical than that of the 1,4-cycloadducts.

The 1,4-adducts *(109)*, which may also be regarded as the thermally inaccessible "Diels-Alder adducts" of naphthalene to *(2)*, can be isolated in good yields by exhaustive irradiation or by use of acetophenone as sensitizer.

Sterically pure *exo* and *endo* 1,2-adducts *(108a)* and *(108b)* regenerate *(2)* and naphthalene quantitatively on direct irradiation. In the presence of sensitizer, however, they undergo >80% stereoselective conversion into the corresponding 1,4-cycloadducts *(109)*. Mechanistic studies reveal the following picture of the naphthalene/*(2)* system:

The 1,2-adducts *(108)* are formed from the S_1 excited state of naphthalene which is trapped by *(2)*. We are therefore dealing with a singlet reaction of naphthalene.

Unlike benzene, naphthalene possesses no degenerate energy levels owing to its lower symmetry. Thus the symmetry disqualification postulated by *Bryce-Smith* for the S_1 state of benzene[101] does not apply to a concerted process from the S_1 state of naphthalene.

Reaction to give the 1,4-cycloadducts *(109)* then takes place from a triplet state of *(108)* which can be occupied either by addition of a sensitizing agent, *e.g.* acetophenone, or by triplet-excited naphthalene itself. (Excited naphthalene has a significant intersystem crossing rate[116] so that 1,4-adducts can also arise in the absence of a sensitizer.) The reason for 1,2-adducts *(108)* not undergoing immediate reversion to naphthalene and *(2)* on direct irradiation is that they absorb at shorter wavelengths than naphthalene and can therefore be largely protected by use of suitable filters.

Hydrolysis of the 1,4-isomer *(109)* affords the diketone *(110)*, which is likewise very stable thermally but is subject to extremely ready photochemical decomposition to naphthalene and carbon monoxide.

8. Conclusion

Observations performed to date on the chemistry of halovinylene carbonates show that this relatively young class of compounds will assume a place among the synthetic reagents of organic chemistry owing to the variety of their possible applications. In spite of the tentative nature of some of the results and a number of unsettled optimization questions, these derivatives have opened the way to molecules whose formation reaction will stimulate further preparative and mechanistic studies.

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[1] *M. S. Newmann* and *R. W. Addor*, J. Amer. Chem. Soc. 75, 1263 (1953).
[2] *H. Kwart* and *W. G. Vosburgh*, J. Amer. Chem. Soc. 76, 5400 (1954).
[3] *M. S. Newmann* and *R. W. Addor*, J. Amer. Chem. Soc. 77, 3789 (1955).
[4] *Y. F. Shealy* and *F. D. Clayton*, J. Amer. Chem. Soc. 91, 3075 (1969).
[5] *C. R. Kowarski* and *S. Sarel*, J. Org. Chem. 38, 117 (1973).
[6] *M. Z. Haq*, J. Org. Chem. 37, 3015 (1972).
[7] *J. B. Lambert* and *A. G. Holcomb*, J. Amer. Chem. Soc. 93, 3952 (1971).
[8] *J. Daub* and *V. Trautz*, Tetrahedron Lett. 1970, 3265.
[9] *R. Criegee* and *P. Becher*, Chem. Ber. 90, 2516 (1957).
[10] *W. Hartmann* and *R. Steinmetz*, Chem. Ber. 100, 217 (1967).
[11] *W. Hartmann*, Chem. Ber. 101, 1643 (1968).
[12] *W. Hartmann*, *H. M. Fischler*, and *H. G. Heine*, Tetrahedron Lett. 1972, 853.
[13] *H. M. Fischler*, *H. G. Heine*, and *W. Hartmann*, Tetrahedron Lett. 1972, 1701.
[14] *J. Tencrede* and *M. Rosenblum*, Chem. Commun. 1971, 219; Synthesis 1971, 219.
[15] *R. H. Grubbs*, J. Amer. Chem. Soc. 92, 6693 (1971).

[16] The oxidation numbers given are those defined by *Pauling*. See *L. Pauling*: Chemie – eine Einführung. 8. Edit., Verlag Chemie, Weinheim 1969, p. 215.

[17] *H. D. Scharf, W. Droste*, and *R. Liebig*, Angew. Chem. *80*, 194 (1968); Angew. Chem. internat. Edit. 7, 215 (1968).

[18] *H. D. Scharf, W. Pinske, M. H. Feilen*, and *W. Droste*, Chem. Ber. *105*, 554 (1972).

[19] *E. K. Ellingboe* and *L. R. Melby*, US-Pat. 2816287 (1957); Chem. Abstr. *52*, 12899g (1958).

[20] *P. Lechtken* and *G. Hesse*, Liebigs Ann. Chem. *754*, 7 (1971).

[21] *J. Fleischhauer* and *H. D. Scharf*, Tetrahedron Lett. *1972*, 1119.

[22] *cis*-Dichloroethylene carbonate is still unknown. Reports of its existence in ref. [3] could not be verified.

[23] *H. D. Scharf, W. D. Busse*, and *W. Pinske*, Chem. Ber. *103*, 3949 (1970).

[24] *W. Pinske*, Dissertation, Technische Hochschule Aachen 1972; Chem. Ber., in press.

[25] *H. D. Scharf* and *W. Küsters*, Chem. Ber. *105*, 564 (1972).

[26] *A. Linckens*, Dissertation, Technische Hochschule Aachen 1973; Chem. Ber., in press.

[27] *O. Diels* and *K. Alder*, Liebigs Ann. Chem. *490*, 243 (1931).

[28] *R. B. Woodward* and *H. Baer*, J. Amer. Chem. Soc. *70*, 1161 (1948).

[29] *J. A. Berson* and *R. Swidler*, J. Amer. Chem. Soc. *75*, 1721 (1953).

[30] *H. Kwart* and *I. Burchuk*, J. Amer. Chem. Soc. *74*, 3094 (1952).

[31] *H. Ishitobi, H. Tanida, K. Tori*, and *T. Tsusi*, Bull. Chem. Soc. Jap. *44*, 2993 (1971).

[32] *H. D. Scharf, W. Küsters*, and *J. Fleischhauer*, Chem. Ber. *104*, 3030 (1971).

[33] *B. Falk*, Diplomarbeit, Technische Hochschule Aachen 1972; Chem. Ber., in press.

[34] *J. Sauer, H. Wiest*, and *A. Mielert*, Chem. Ber. *97*, 3183 (1964).

[35] *J. Sauer*, Angew. Chem. *79*, 76 (1967); Angew. Chem. internat. Edit. *6*, 16 (1967).

[36] *J. Fleischhauer*, lecture at Chemiedozententagung 1973, Münster.

[37] *K. Fukui*, Fortschr. Chem. Forsch. *15*, 1 (1970).

[38] *L. Salem*, J. Amer. Chem. Soc. *90*, 553 (1968).

[39] *R. Hoffmann*, J. Chem. Phys. *39*, 1397 (1963).

[40] *K. Alder*, Experientia Suppl. *2*, 86 (1955).

[41] *W. E. Bachmann* and *N. C. Deno*, J. Amer. Chem. Soc. *71*, 3062 (1949).

[42] *J. Fleischhauer*, personal communication.

[43] *R. F. Hudson*, Angew. Chem. *85*, 63 (dort 65) (1973); Angew. Chem. internat. Edit. *12*, 36 (1973).

[44] *K. Alder* and *G. Stein*, Angew. Chem. *50*, 510 (1937).

[45] M. p. 78 –79 °C: *G. A. Russel, G. W. Holland*, and *K. Y. Chang*, J. Amer. Chem. Soc. *89*, 6629 (1967).

[46] M. p. 200 °C: *J. Strating, B. Zwanenburg, A. Wagenaar*, and *A. C. Udding*, Tetrahedron Lett. *1969*, 125.

[47] M. p. 199–201.5 °C: *W. R. Vanghan* and *M. Yoshimine*, J. Org. Chem. *22*, 528 (1957).

[48] M. p. 87– 88 °C: *H. J. Teuber* and *G. Staiger*, Chem. Ber. *88*, 802 (1955).

[49] A value of 35 °C was originally given [17]. The sample was not completely pure.

[50] *H. Staudinger* and *E. Anthes*, Ber. Deut. Chem. Ges. *46*, 1426 (1913).

[51] See also *L. Horner* and *H. Merz*, Liebigs Ann. Chem. *570*, 89 (1950).

[52] A mass peak of *m/e* 56 is given in ref. [46] as occurring in the MS spectrum of *(45)*. It is assigned to C_2O_2.

[53] *J. Fleischhauer, M. Beckers*, and *H. D. Scharf*, Tetrahedron Lett., in press.

[54] *H. D. Breuer, H. Moesta*, and *N. Trappen*, Chem.-Ztg. *94*, 129 (1970).

[55] *H. D. Scharf* and *W. Küsters*, Chem. Ber. *104*, 3016 (1971).

[56] *G. O. Schenck* and *R. Steinmetz*, Chem. Ber. *96*, 520 (1963).

[57] *D. I. Schuster, M. Exelrod*, and *J. Auerbach*, Tetrahedron Lett. *1963*, 1911.

[58] *D. E. Bays* and *R. C. Cookson*, J. Chem. Soc. *B 1967*, 226.

[59] *P. Yates* and *L. Kilmurry*, Tetrahedron Lett. *1964*, 1739.

[60] *J. Ipaktschi*, Chem. Ber. *105*, 1840 (1972); Tetrahedron Lett. *1969*, 3179.

[61] *M. H. Feilen*, Dissertation, Technische Hochschule Aachen 1972.

[62] ^{1}H-NMR analysis performed by *D. Wendisch*, Bayer AG, Leverkusen.

[63] *A. Linckens*, Diplomarbeit, Technische Hochschule Aachen 1971.

[64] *R. W. Hoffmann*, Angew. Chem. *80*, 823 (1968); Angew. Chem. internat. Edit. 7, 754 (1968).

[65] *J. Mattay*, Diplomarbeit, Technische Hochschule Aachen 1972.

[66] *H. D. Scharf* and *H. Seidler*, Angew. Chem. *82*, 935 (1970); Angew. Chem. internat. Edit. 9, 900 (1970).

[67] *R. West, H. Y. Niu*, and *M. Ito*, J. Amer. Chem. Soc. *85*, 2584 (1963).

[68] *R. Nietzki et al.*, Ber. Deut. Chem. Ges. *19*, 293 (1886); *18*, 499 (1885).

[69] *H. D. Scharf* and *P. Klar*, Liebigs Ann. Chem. *739*, 166 (1970).

[70] *H. D. Scharf, W. Erb, H. W. Borsdorff*, and *D. Wendisch*, Chem. Ber. *106*, 1695 (1973).

[71] *W. Droste*, Dissertation, Universität Bonn 1968.

[72] *W. G. Herkstroeter, A. A. Lamola*, and *G. S. Hammond*, J. Amer. Chem. Soc. *86*, 4537 (1964).

[73] *R. F. Borkman* and *D. R. Kearns*, J. Chem. Phys. *44*, 945 (1966).

[74] *J. Fleischhauer, H. Thiele*, and *H. Leismann*, Z. Naturforsch., in press.

[75] *W. Gaidetzka*, Dissertation, Technische Hochschule Aachen 1975.

[76] *H. Leismann* and *J. Berix*, Z. Naturforsch., in press.

[77] For recent results, see *W. Hartmann, H.-G. Heine*, and *W. Schrader*, Tetrahedron Lett. *1974*, 883.

[78] *G. Ciamician* and *P. Silber*, Ber. Deut. Chem. Ges. *44*, 1554 (1911).

[79] *St. C. Neely, R. Fink, D. van der Helm*, and *J. J. Bloomfield*, J. Amer. Chem. Soc. *93*, 4903 (1971).

[80] *J. J. Bloomfield*, Tetrahedron Lett. *1968*, 587.

[81] *K. Rühlmann*, Synthesis *1971*, 236.

[82] *J. J. Bloomfield, J. R. S. Irelan*, and *A. P. Marchand*, Tetrahedron Lett. *1968*, 5647.

[83] *A. de Groot, D. Oudman*, and *H. Wynberg*, Tetrahedron Lett. *1969*, 1529.

[84] *J. M. Conia* and *J. M. Denis*, Tetrahedron Lett. *1971*, 2845.

[85] *H. G. Heine*, Chem. Ber. *104*, 2869 (1971).

[86] *W. Erb*, Dissertation, Technische Hochschule Aachen 1974. The cycloadduct of *(2)* and 1,2-dimethyl-1-cyclohexene has meanwhile been hydrolyzed to 1,6-dimethylbicyclo[4.2.0]octane-7,8-dione.

[87] See also refs. [84], [82], and [85].

[88] *H. G. Heine*, Bayer AG, Uerdingen-Krefeld, personal communication.

[89] *C. K. Ingold, S. Sako*, and *J. F. Thorpe*, J. Chem. Soc. *121*, 177 (1922).

[90] *J. Knops*, Diplomarbeit, Technische Hochschule Aachen 1972.

[91] In contrast, *Kuhn* and *Gollnik* observed secondary products of the initial [4+2] adduct during thermal and photochemical diene syntheses with thiophene. *H. J. Kuhn* and *K. Gollnik*, Tetrahedron Lett. *1972*, 1909; Chem. Ber. *106*, 674 (1973).

[92] *J. C. Hinshaw*, Chem. Commun. *1971*, 630.

[93] *H. D. Scharf* and *H. Seidler*, Chem. Ber. *104*, 2995 (1971).

[94] *A. T. Blomquist* and *R. A. Vierling*, Tetrahedron Lett. *1961*, 655; US-Pat. 3169147 (1965); Chem. Abstr. *62*, 16081 (1965).

[95] For an alternative synthesis, see *E. V. Dehmlow*, Chem. Ber. *100*, 3892 (1967).

[96] *H. J. F. Angus* and *D. Bryce-Smith*, Proc. Chem. Soc. *1959*, 326.

[97] *G. O. Schenck* and *R. Steinmetz*, Tetrahedron Lett. *1960*, No. 21, p. 1.

[98] *E. Grovenstein, jr., D. V. Rao*, and *J. W. Taylor*, J. Amer. Chem. Soc. *83*, 1705 (1961).

[99] For a review, see *D. Bryce-Smith*, Pure Appl. Chem. *16*, 47 (1968); 2nd IUPAC Symposium on Organic Photochemistry, Enschede 1967.

[100] *W. M. Hardham* and *G. S. Hammond*, J. Amer. Chem. Soc. *89*, 3200 (1967).

[101] *D. Bryce-Smith*, Pure Appl. Chem. *34*, 193 (1973).

[102] *N. C. Yang* and *J. Libman*, Tetrahedron Lett. *1973*, 1409.

[103] *K. E. Wilzbach* and *L. Kaplan*, J. Amer. Chem. Soc. *93*, 2073 (1971).

[104] *N. C. Yang, J. Libman*, and *M. F. Savitzky*, J. Amer. Chem. Soc. *94*, 9226 (1972).

[105] *N. C. Yang* and *J. Libman*, J. Amer. Chem. Soc. *94*, 9228 (1972).

[106] *J. J. McCullough, C. Calvo*, and *C. W. Huang*, Chem. Commun. *1968*, 1176.

[107] *R. M. Bowman* and *J. J. McCullough*, Chem. Commun. *1970*, 948.

[108] *D. R. Arnold, L. B. Gillis*, and *E. B. Whipple*, Chem. Commun. *1969*, 918.

[109] *D. Bryce-Smith*, Chem. Commun. *1969*, 806.

[110] *P. Lechtken* and *G. Hesse*, Liebigs Ann. Chem. *754*, 1 (1971).

[111] *H. D. Scharf* and *R. Klar*, Tetrahedron Lett. *1971*, 517.

[112] *H. D. Scharf* and *R. Klar*, Chem. Ber. *105*, 575 (1972).

[113] *G. Hesse* and *P. Lechtken*, Angew. Chem. *83*, 143 (1971); Angew. Chem. internat. Edit. *10*, 133 (1971).

[114] *S. Yankelevich* and *B. Fuchs*, Tetrahedron Lett. *1967*, 4945.

[115] *J. Aretz*, Dissertation, Technische Hochschule Aachen 1973; Chem. Ber., in press.

[116] Population of the naphthalene triplet *via* intersystem crossing amounts to $\Phi_{isc}=0.39$. *J. G. Calvert* and *J. N. Pitts*: Photochemistry. Wiley, New York 1966, p. 309.

[117] M.p. 163 °C (dec.). IR (KBr): ν_{CO}: 1890, 1800, 1740 cm^{-1}; ν_{OH}: 2800–2200 cm^{-1}; $\nu_{=C-H}$: 3150 cm^{-1}. ^{1}H-NMR (15 mg *(62)*/0.5 ml [D_6]-acetone): $\tau=1.19$ (1H, s), 2.53 (1H, s). MW (MS): 98. UV [ether, nm (ε)]: 213 (16404), 231 (8154), 308.5 (23.7), 371 (14.5); UV [H_2O, 1.98×10^{-5} M; nm (ε)]: 257.5 (8283), 227 (28636); [H_2O, 9.9×10^{-3} M; nm (ε)]: 382 (9.4).

[118] Semisquaric acid *(62)* has been prepared by *R. W. Hoffmann, U. Bressel, I. Gehlhaus*, and *H. Häuser*, Chem. Ber. *104*, 873 (1971), by an alternative route.

[119] *R. I. Cole, I. W. Kirksey, H. G. Cutler, B. L. Donpink*, and *I. C. Peckham*, Science *179*, 1324 (1973).

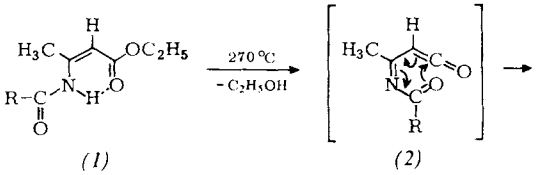
[120] *I. P. Springer, I. Clardy, R. I. Cole, I. W. Kirksey, R. K. Hill, R. M. Carbon*, and *I. L. Isidor*, J. Amer. Chem. Soc. *96*, 2267 (1974).

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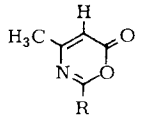
Reaction of 1,3-Oxazin-6-ones with Ynamines and Ketene *N,O*-Acetals

By Wolfgang Steglich, Ernst Buschmann, and *Oswald Hollitzer*[*]

1,3-Oxazin-6-ones *(3)*[1] open up interesting preparative prospects that have hitherto been little explored. We have found that 4-methyl-1,3-oxazin-6-pnes *(3a)—(3c)* (Table 1) can be prepared from 2-(acylamino)crotonic esters *(1)* by heating them in a metal-bath at 270 °C and distilling off the alcohol that is formed[2]; the reaction may occur by way of ketene intermediates *(2)*[3].



(1) *(2)*



(3)

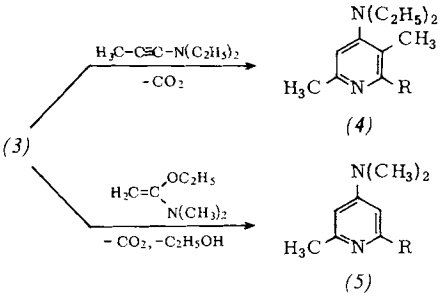
Table 1. 4-Methyl-1,3-oxazin-6-ones *(3)* prepared [a].

Cpd.	R	Yield [%]	B.p. [°C/torr]
(3a)	$(CH_3)_2CH$	65	40—42/0.1
(3b)	$(CH_3)_2CHCH_2$	40	47—49/0.15
(3c)	$(CH_3)_3C$	60	39—41/0.3
(3d) [b]	CF_3	52	66—69/12

[a] All the compounds gave correct elemental analyses.
[b] From *tert*-butyl 3-aminocrotonate and trifluoroacetic anhydride.

The 2-trifluoromethyl derivative *(3d)* was obtained from *tert*-butyl 3-aminocrotonate by the action of trifluoroacetic anhydride at room temperature. The 1,3-oxazinones *(3a)—(3c)* show characteristic bands in the IR spectrum (CCl_4) at 1770, 1632 and 1580 cm^{-1} [*(3d)*: 1795, 1655 and 1595 cm^{-1}] and NMR signals for the methyl group and the vinyl protons at $\delta=2.18$ (d, $J=1$ Hz) and 5.9 (q, $J=1$ Hz), respectively [*(3d)*: $\delta=2.38$ and 6.25].

Reaction of the 1,3-oxazinones with *N,N*-diethyl-1-propynamine affords 2,3,6-trisubstituted 4-(diethylamino)pyridines *(4)*; and 2,6-disubstituted 4-(dimethylamino)pyridines *(5)* are formed on reaction with 1-ethoxy-*N,N*-dimethylvinylamine[4] (Table 2). The reactions of *(3a)—(3c)* in ether are complete within a few hours, but cooling is necessary with *(3d)* because of the strong evolution of heat.



(4) *(5)*

Table 2. 4-(Dialkylamino)pyridines *(4)* and *(5)* prepared [a].

Cpd.	R	Yield [%]	B.p. [°C/torr]	M.p. [°C]
(4a)	$(CH_3)_2CH$	79	64—66/0.2	
(4b)	$(CH_3)_2CHCH_2$	89	77—78/0.2	
(4c)	$(CH_3)_3C$	65	78/0.1	
(4d)	CF_3	67	66—68/0.2	
(5a)	$(CH_3)_2CH$	80	63—64/0.2	
(5b)	$(CH_3)_2CHCH_2$	90	78—79/0.1	
(5c)	$(CH_3)_3C$	94		73
(5d)	CF_3	80		75.5

[a] All the compounds gave correct elemental analyses.

The orientation of the substituents follows from the NMR spectra. Thus *(4d)* shows an H,F coupling of 2.3 Hz between the trifluoromethyl group and the methyl group in position 3. For the *tert*-butyl derivative *(5c)* the aromatic protons appear as an AB quartet at $\delta=6.20$ and 6.37 ($J=2.5$ Hz) but for *(5a)* and *(5b)* as a single signal. The 2-trifluoromethyl group in *(5d)* causes a shift of the AB quartet to $\delta=6.52$ and 6.79.

Their diene character determines the course of reaction of 1,3-oxazinones with electron-rich multiple bonds, whereas with 3,1-benzoxazinones the anhydride system from carboxylic and imidic acids also plays an important part[5]. The regiospecificity observed corresponds to attack by the nucleophile on the C=N group of this system.

2-tert-Butyl-4-methyl-1,3-oxazin-6-one (3c)

Ethyl 3-(pivaloylamino)crotonate (105 g) *(1c)* was heated for 3 h in a metal bath at 270 °C, the ethanol formed distilling off through an air-condenser. Distillation in a high vacuum afforded a colorless oil (49 g, 60%).

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2-tert-Butyl-4-(dimethylamino)-3,6-dimethylpyridine (4)

N,N-Dimethyl-1-propynylamine (2.5 g) in anhydrous ether (10 ml) is dropped into *(3c)* (3.34 g) in ether (20 ml) at room temperature. After 4 hours' stirring, the mixture is extracted with 1 N HCl, the aqueous phase is neutralized with 1 N KOH and extracted with ether, and the extract is dried over $MgSO_4$. After removal of the solvent the residue is distilled in a high vacuum. Yield 3.05 g (65%).

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[1] *C. C. Barker*, J. Chem. Soc. *1954*, 317; *V. Sprio*, Gazz. Chim. Ital. *85*, 569 (1955); *H. B. Kagan* and *Y-Heng Suen*, Bull. Soc. Chim. Fr. *1966*, 1819; *T. Sasaki, K. Kanematsu*, and *A. Kakehi*, J. Org. Chem. *36*, 2451 (1971).

[2] *F. Eiden* and *B. S. Nagar*, Naturwissenschaften *50*, 403 (1963), cyclized 3-(acylamino)-2-arylacrylic esters to 1,3-oxazinones by heating them in high-boiling solvents. With more volatile oxazinones such as *(3a)*–*(3c)* this leads to difficulties in separation.

[3] Cf. the course of the Conrad-Limpach reaction: *H. M. Blatter* and *H. Lukaszewski*, Tetrahedron Lett. *1964*, 855. Similar electrocyclizations: *E. Ziegler* and *H. Meindl*, Monatsh. Chem. *95*, 1318 (1964); *H. R. Kricheldorf*, Angew. Chem. *84*, 107 (1972); Angew. Chem. internat. Edit. *11*, 128 (1972); *J. H. McMillan* and *S. S. Washburne*, J. Org. Chem. *38*, 2982 (1973).

[4] For the use of ketene *N,O*-acetals in Diels-Alder reactions with inverse electron demand cf. *J. Sauer* and *G. Heinrichs*, Tetrahedron Lett. *1966*, 4979; 4-dialkylaminopyridines from 1,2,4-triazines and ketone *O,N*-acetals: *H. Neunhoeffer* and *H. W. Frühauf*, Liebigs Ann. Chem. *758*, 120 (1972).

[5] *G. Höfle, O. Hollitzer*, and *W. Steglich*, Angew. Chem. *84*, 716 (1972); Angew. Chem. internat. Edit. *11*, 720 (1972); *W. Steglich* and *O. Hollitzer*, Angew. Chem. *85*, 505 (1973); Angew. Chem. internat. Edit. *12*, 495 (1973).

Photochemical Synthesis of Bis(η-methyl acrylate)tricarbonyliron

By *Friedrich-Wilhelm Grevels, Dorothea Schulz*, and *Ernst Koerner von Gustorf*[*]

Electronic excitation of an olefintetracarbonyliron complex can lead both to cleavage of the olefin-iron bond and to elimination of CO[1].

$$LFe(CO)_4 \xrightarrow{h\nu} \begin{cases} \xrightarrow{a)} CO + LFe(CO)_3 \\ \xrightarrow{b)} L + Fe(CO)_4 \end{cases}$$

The coordinatively unsaturated olefintricarbonyliron species formed according to a) should react with an excess of olefin (L) to give the hitherto unknown[2] bis(olefin)tricarbonyliron $L_2Fe(CO)_3$; the tetracarbonyliron formed according to b) reacts with L to regenerate the starting material.

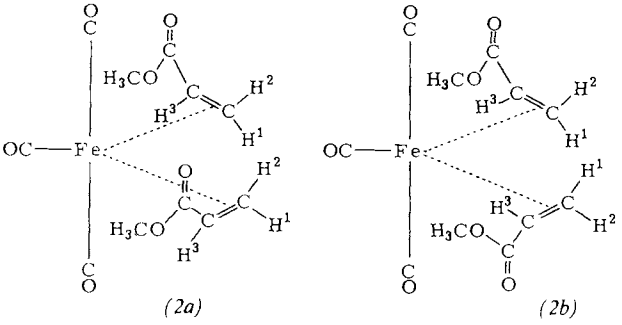
Irradiation of (η-methyl acrylate)tetracarbonyliron *(1)* in the presence of excess methyl acrylate in *n*-hexane at −30 °C thus generates bis(η-methyl acrylate)tricarbonyliron *(2)*, which we were able to isolate as a light yellow solid that is stable for an extended period at −78 C.

$$\underset{(1)}{(CH_2\text{-}CH\text{-}COOCH_3)Fe(CO)_4} + CH_2{=}CH\text{-}COOCH_3 \xrightarrow[\text{hexane}]{h\nu,\ -30\,^\circ C} \underset{(2)}{(CH_2{=}CH\text{-}COOCH_3)_2Fe(CO)_3} + CO \quad (1)$$

The composition of *(2)* follows from elemental analysis and the mass spectrum which shows the molecular ion ($m/e = 312$) and the successive loss of 3 CO ($m/e = 284, 256, 228$) as well as the elimination of one methyl acrylate molecule ($m/e = 226$) and the subsequent loss of 3 CO ($m/e = 198, 170, 142$) at a vaporization temperature of −30 C.

In the IR spectrum (*n*-hexane, −30 C) of *(2)* three bands appear in the metal carbonyl stretching region at 2087 (vw, $A_1^{(1)}$), 2024 (vs, B_1), and 2012 cm^{-1} (s, $A_1^{(2)}$) whose intensity ratio indicates that both olefinic ligands occupy equatorial positions in the trigonal bipyramidal complex (C_{2v} local symmetry)[3].

The ^{1}H-NMR spectrum (Table 1) shows two sets of signals whose intensity ratio depends upon the temperature and work-up conditions, thus indicating the presence of two isomers *(2a)* and *(2b)* in which the corresponding protons of the two methyl acrylate ligands are equivalent. We succeeded in recording the spectrum of pure *(2a)*.



(2a) *(2b)*

Table 1. ^{1}H-NMR data of the isomeric complexes *(2)* (0.4 M in [D_8]-toluene, −31 C).

	τ [ppm]				Coupling constants [Hz]		
	H^1	H^2	H^3	H^{CH_3}	J_{12}	J_{13}	J_{23}
(2a)	7.58	6.78	6.48	6.59	<1	6.5	12
(2b)	7.38	6.98	6.74	6.62	<1	6.5	12

Assuming rotation to occur about the metal-olefin bond axis[4], then other conceivable isomers are merely conformers of *(2a)* or *(2b)*. Assignment of structures is based on the ^{1}H-NMR spectra: the anisotropic effect of the ester carbonyl groups on the vinyl protons of the other olefin ligand should lead to a downfield shift for H^1 and an upfield shift for H^2 and H^3 on going from *(2a)* to *(2b)* (assuming coplanarity of the C=O and C=C bond planes as indicated in the formulas[5]).

On warming to 0 C pure *(2a)* (0.4 M) undergoes partial conversion into *(2b)*, yielding equal concentrations of the two isomers; this isomerization *(2a)* → *(2b)* requires temporary cleavage of an iron-olefin bond.

On heating of a dilute solution (0.003 M) of *(2)* in *n*-hexane from −30 to −5 °C the IR bands of *(2)* largely disappear and are replaced by three new bands at 2064 (m), 1994 (s), and 1979 cm^{-1} (s). The process can be reversed by addition of methyl acrylate, thus showing that at this temperature the complex *(2)* can reversibly loose an olefin ligand and is in equilibrium with (methyl acrylate)tricarbonyliron *(3)*.

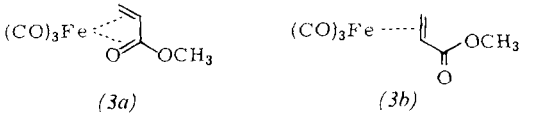
$$\underset{(2)}{} \xrightleftharpoons{-5\,^\circ C} \underset{(3)}{(CH_2{=}CH\text{-}COOCH_3)Fe(CO)_3} + CH_2{=}CH\text{-}COOCH_3 \quad (2)$$

We have not yet been able to isolate *(3)* in pure form. Since its IR spectrum resembles those of tricarbonyliron complexes of α,β-unsaturated ketones[6] with regard to intensity distribution and splitting pattern of the M(C≡O) bands we tend

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[**] We are grateful to Dr. J. Leitich for his assistance in the discussion of the ^{1}H-NMR spectra.

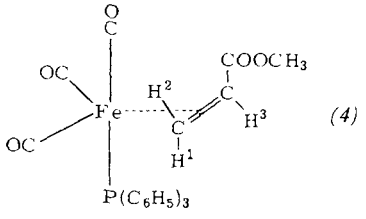
to favor structure *(3a)* in which the α,β-unsaturated ester is coordinated as a 1-oxabutadiene system[7].



(3a) *(3b)*

It may be expected that *(3a)* is readily transformed into *(3b)* and behaves *de facto* as a coordinatively unsaturated species since an ester group generally displays little inclination to coordinate to metal(0)[7]. A small amount of *(3b)* might possibly be present in equilibrium with *(3a)*.

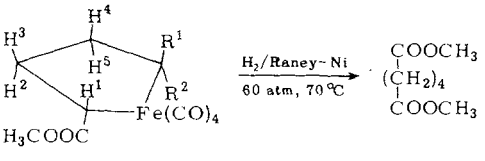
On warming to 20 C under a CO atmosphere complex *(2)* regenerates *(1)*; reaction with triphenylphosphane affords (η-methyl acrylate)tricarbonyl(triphenylphosphane)iron *(4)*[8] (cf. equilibrium (2)). X-Ray structure analysis[9] of *(4)* shows that the largely σ-bonded phosphane ligand occupies the axial position[10] and the π-bonded olefin ligand the equatorial position in the trigonal bipyramid.



(4)

(2)⇌*(3)* provides a means of studying the chemistry of L—Fe(CO)$_3$, an important primary photolysis product of L—Fe(CO)$_4$, "in the dark". The formation of LFe(CO)$_3$ as an intermediate in complex photochemical reactions of LFe(CO)$_4$ can be regarded as proven if reaction of a particular substance with *(2)* "in the dark" and with LFe(CO)$_4$ upon irradiation yields the same product[11].

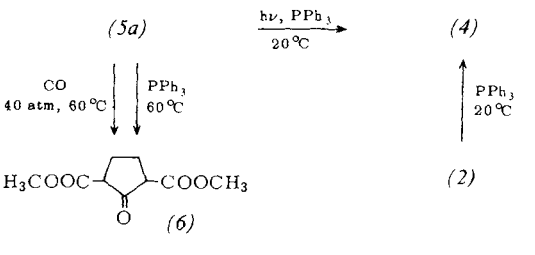
If *(1)* (0.05 M) and methyl acrylate (0.5 M) in hexane are irradiated, not at −30 C, but at +20 C, then instead of 1 mol only 1/3 of a mol of CO is released per mol of *(1)* and the reaction comes to a halt after conversion of about 50% of *(1)*, due to the back reaction of *(2)* with CO. About 20% of the reacted *(1)* affords two isomeric complexes having the composition $(C_4H_6O_2)_2Fe(CO)_4$. IR, ^{1}H-NMR, and mass spectra[12] show them to be dimethyl *trans-* and *cis*-1,1,1,1-tetracarbonylferracyclopentane-2,5-dicarboxylate *(5a)* and *(5b)*, respectively, of which *(5a)* predominates.



(5a), $R^1 = COOCH_3$, $R^2 = H^6$
(5b), $R^1 = H^6$, $R^2 = COOCH_3$

Both compounds can be hydrogenated to dimethyl adipate by H_2/Raney nickel.

Thermal reaction of *(5a)* with CO affords dimethyl cyclopentanone-2,5-dicarboxylate *(6)*, while heating with PPh_3 likewise furnishes *(6)* as well as tricarbonylbis(triphenylphosphane)iron. The C—C bond produced during formation of *(5)* can be ruptured again photochemically. Compound *(4)* results from irradiation of *(5)* in the presence of PPh_3. Dimethyl *trans*-2-hexen-1,6-oate and its Fe(CO)$_4$ complex were also isolated as products of a hydrogen shift.



(5a) *(4)* *(6)* *(2)*

Compounds such as *(2)* and *(5)* have recently been proposed as intermediates in the photochemical formation of cyclopentanones from Fe(CO)$_5$ and cyclic olefins[13]. Indeed, we were able to show that *(5)* is formed thermally from *(2)* and reacts with CO yielding the cyclopentanone derivative *(6)*. These results again demonstrate the value of low temperature photolysis for the elucidation of reaction mechanisms. We shall report separately on the reaction step inducing the C—C linkage formation[14].

Procedure:

A solution of *(1)* (2.54 g, 0.01 mol) and methyl acrylate (8.6 g, 0.10 mol) in hexane (200 ml) was irradiated for 4.5 h at −30 C in an immersed lamp apparatus (Solidex glass, high-pressure mercury lamp Philips HPK 125 W), whereupon 1.02 mol of CO were liberated per mol of *(1)*. Compound *(2)* precipitates as light yellow crystals within 2–3 days at −78 C; the crystals were separated by inverse filtration and dried in an oil-pump vacuum at −30 °C[15]. Yield: 2.72 g (87%).

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[1] *F.-W. Grevels, D. Schulz*, and *E. A. Koerner von Gustorf*, VII. Int. Conf. Photochem., Jerusalem 1973, Abstr. p. 57; *J. Buchkremer, F.-W. Grevels, O. Jaenicke, P. Kirsch, R. Knoesel, E. A. Koerner von Gustorf*, and *J. Shields, ibid.* p. 61; *E. A. Koerner von Gustorf, J. Buchkremer, F.-W. Grevels, J. M. Kelly*, and *R. Knoesel*, 164th Nat. Meeting Amer. Chem. Soc., New York 1972, Abstr. Inor 44.

[2] *M. Herberhold*: Metal π-Complexes, Vol. II 1, Elsevier, Amsterdam 1972. A complex initially designated as tricarbonylbis(η-tetrafluoroethylene)iron proved to be 1,1,1,1-tetracarbonyloctafluoroferracyclopentane; the bis(tetrafluoroethylene) complex may occur as an intermediate. *K. F. Watterson* and *G. Wilkinson*, Chem. Ind. (London) *1959*, 991; *1960*, 1358; *R. Fields, M. M. Germain, R. N. Haszeldine*, and *P. W. Wiggans*, J. Chem. Soc. A *1970*, 1969.

[3] A square pyramidal *trans*-bis(olefin) complex would also possess local C_{2v} symmetry and give a similar spectrum. However, no such deviation from a trigonal bipyramidal structure has yet been found in the series of Fe^0 complexes having unidentate ligands only.

[4] *R. Cramer*, J. Amer. Chem. Soc. *86*, 217 (1964); *B. F. G. Johnson* and *J. A. Segal*, J. C. S. Chem. Commun. *1972*, 1312.

[5] X-Ray structure analysis of carbonylbis(2-5-η-methyl sorbate)iron indicates that the ester carbonyl group and the diene unit are largely coplanar: *C. Krüger* and *Y. H. Tsay*, to be published.

[6] *E. Koerner von Gustorf, F.-W. Grevels, C. Krüger, G. Olbrich, F. Mark, D. Schulz*, and *R. Wagner*, Z. Naturforsch. *B 27*, 392 (1972).

[7] *E. Koerner von Gustorf, O. Jaenicke*, and *O. E. Polansky*, Z. Naturforsch. *B 27*, 575 (1972); *T. Kruck* and *L. Knoll*, Chem. Ber. *106*, 3578 (1973).

[8] Light yellow crystals, dec. 120–125 C. ^{1}H-NMR ($CDCl_3$, 0 C): τ = 8.62 (H^1), 7.34 (H^2), 7.48 (H^3), 6.33 (H^{CH_3}), 2.4–2.7 ppm ($H^{C_6H_5}$); $J_{12} < 1$, $J_{13} = 7$, $J_{2A} = 11.4$, $J_{1P} = 5.4$, $J_{2P} = 7$, $J_{AP} = 7.8$ Hz. IR (*n*-hexane): metal-carbonyl region: ν̃ = 2042.5, 2035, 1981, 1975, 1945 cm^{-1}; ester-carbonyl region: ν̃ = 1710 cm^{-1}.

[9] *C. Krüger* and *Y. H. Tsay*, to be published.

[10] *E. H. Schubert* and *R. K. Sheline*, Inorg. Chem. *5*, 1071 (1966); *H. Haas* and *R. K. Sheline*, J. Chem. Phys. *47*, 2996 (1967); *M. L. Ziegler*, Angew. Chem. *80*, 239 (1968); Angew. Chem. internat. Edit. *7*, 222 (1968).

[11] *E. Koerner von Gustorf, M. K. Das*, and *F.-W. Grevels*, unpublished; *F.-W. Grevels* and *E. Koerner von Gustorf*, in press.

[12] *(5a)*: pale yellow crystals, m.p. 133–135 C (dec.). ^{1}H-NMR (C_6D_6): τ ≈ 6.8–7.1 (H^1, H^6), 8.0–8.3 (H^2, H^3, H^4, H^5), 6.60 ppm (H^{CH_3}). IR (*n*-hexane): metal-carbonyl region: ν̃ = 2115.5, 2056, 2047, 2034 (sh), 2029.5 cm^{-1}; ester-carbonyl region: ν̃ = 1714 cm^{-1}.—*(5b)*: pale yellow crystals, m.p. 114 to 115 C (dec.). ^{1}H-NMR: τ ≈ 7.0–7.2 (H^1, H^6), 7.5–7.8 (H^2, H^5), 8.4–8.8 (H^3, H^4), 6.64 ppm (H^{CH_3}). IR: ν̃ = 2114.5, 2062, 2043, 2032, 1718 cm^{-1}. The molecular ion (*m/e* = 340) cannot be detected in the mass spectrum of either

compound. However, the fragments $[M-OCH_3]$ ($m/e = 309$) and $[M-CO]$ ($m/e = 312$) are observed as well as successive elimination of further CO. On the basis of the ^{1}H-NMR spectra we have assigned the *trans* arrangement of ester groups to *(5a)* and the *cis* arrangement to *(5b)* since for the latter a splitting of the methylene proton signals into two groups would be more likely than for the *trans* compound. This assignment has been confirmed by an X-ray structure analysis of *(5a)* (*C. Krüger* and *Y. H. Tsay*, to be published).

[13] *J. Grandjean, P. Laszlo*, and *A. Stockis*, J. Amer. Chem. Soc. *96*, 1622 (1974); *J. Mantzaris* and *E. Weissberger*, *ibid.* *96*, 1873, 1880 (1974).

[14] *F.-W. Grevels, B. E. Foulger, J. Leitich*, and *E. Koerner von Gustorf*, to be published.

[15] $(C_4H_6O_2)_2Fe(CO)_3$ (312.1); calc. C 42.34, H 3.88, Fe 17.90; found C 42.45, H 3.85, Fe 17.90.

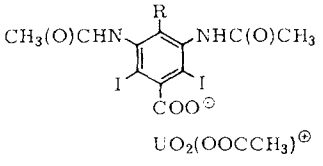
Structural Analysis by Direct Observation of Atoms by Dark Field Transmission Electronmicroscopy[**]

By *Robert F. Whiting, F. Peter Ottensmeyer*, and *Frederick C. Nachod*[*]

The most desirable method for the determination of chemical structure is the direct visualization of the atoms of a molecule. X-ray diffraction analysis can accurately map the positions of the atoms in a molecule but this technique is not routinely available. Chemical structural analysis usually relies on synthetic and spectrometric procedures which are highly sophisticated but are necessarily indirect. There is always a measure of reasonable doubt in the results obtained.

Recently it has been shown that single heavy atoms can be imaged in the electron microscope by a variety of techniques[1]. In particular, atoms ranging in atomic number from 46 (Pd) to 92 (U) have been directly imaged in a number of compounds by dark field electron microscopy in our laboratory[2]. The resolving power of the electron microscope (Philips EM 300) was shown to be better than 3 Å. Since this is within the range of atomic separations for the larger atoms in molecules, it led us to consider the possibility of structural analysis of some characteristic compounds containing heavy atoms. This communication reports the use of high resolution dark field electron microscopy to confirm the structure of a diiodobenzoic acid derivative.

In an investigation of urographic radiopaques, *Larsen et al.*[3] synthesized a 3,5-bis(acetamido)diiodobenzoic acid which, on the basis of analysis of its synthetic relationships to known compounds, was assigned the structure of the 2,6-diiodo isomer; other data, such as NMR findings, were ambiguous. Along with the diiodobenzoic acid, a sample of 3,5-bis(acetamido)-2,4,6-triiodobenzoic acid was used as a control in the study. For the electron microscopic investigation these acids were converted into the acetatouranyl(VI) salts *(1)* and *(2)*



$UO_2(OOCCH_3)^{\oplus}$

(1), R = H
(2), R = I

respectively, by "staining" the carboxyl group with a uranyl acetate [12 hours stirring, 0.05 N uranyl acetate, 0.05 N HCl (pH 3.5), filtration (0.22 μ Millipore filter)].

The sample solution was applied to a pretreated 10—20 Å thick film of carbon and examined by dark field electron microscopy in a Philips EM 300 (80 kV; magnification $10^5\times$). Dark field illumination was obtained by beam tilt. Details of these techniques have been described elsewhere[2]. The electron micrographs of *(1)* and *(2)* (Figure 1) show the relationship of the position of the iodine atoms (lighter dots) to that of the uranium atom (dark dot). Only the heavier atoms in the molecules are observable. Atoms as light as carbon scatter too few electrons to produce a signal strong enough to stand out above the electron noise and the random structure of the support film. The slight differences in geometry in the images generally observed are thought to be due to small disarrangement of the atoms caused by the intense electron bombardment of the molecule in the microscope at the time of exposure of the image. Nevertheless the numbers, geometry and separations of the spots are entirely consistent with the basic molecular structure (cf. particularly Fig. 1b).

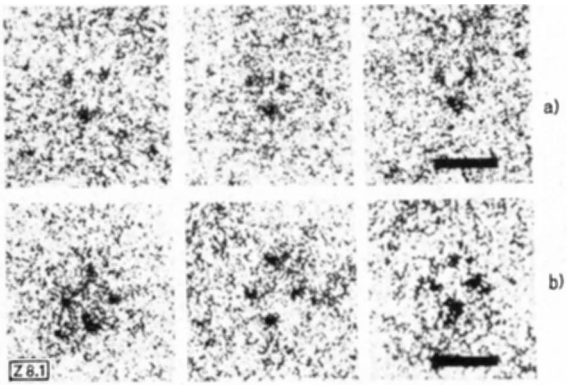


Fig. 1. Dark field electron micrographs of uranyl stained 3,5-bis(acetamido)-2,6-diiodobenzoic acid *(1)*, and uranyl stained 3,5-bis(acetamido)-2,4,6-triiodobenzoic acid *(2)*. In each image only the iodine and uranium atoms are visible. The images have been oriented such that the uranium atom is on the bottom. The bars represent 10 Å.

Thus, a structure derived by chemical analysis has been verified by dark field electron microscopy. The technique is straightforward and, assuming the necessary expertise has been acquired, takes about half a day to complete. At present compounds are restricted to those containing heavy atoms to be used as positional markers, although atoms as light as sulphur have been detected by use of such markers in conjunction with signal averaging of many images[4].

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[1] *R. M. Henkelman* and *F. P. Ottensmeyer*, Proc. Nat. Acad. Sci. U.S.A. *68*, 3000 (1971); *H. Hashimoto, A. Kumao, K. Hino, H. Yatsumoto*, and *A. Ono*, Jap. J. Appl. Phys. *10*, 1115 (1971); *H. Formanek, M. Müller, M. H. Hahn*, and *T. Koller*, Naturwissenschaften *58*, 339 (1971); *A. V. Crewe, J. Wall*, and *J. Langmore*, Science *168*, 1338 (1970).

[2] *R. F. Whiting* and *F. P. Ottensmeyer*, J. Mol. Biol. *67*, 173 (1972).

[3] *A. A. Larson, C. Moore, J. Sprague, B. Cloke, J. Moss*, and *J. O. Hoppe*, J. Amer. Chem. Soc. *78*, 3210 (1956).

[4] *F. P. Ottensmeyer, E. E. Schmidt*, and *A. J. Olbrecht*, Science *179*, 175 (1973); *F. P. Ottensmeyer, E. E. Schmidt, T. Jack*, and *J. Powell*, J. Ultrastruct. Res. *40*, 546 (1972).

The Contact Contribution in the Lanthanoid-Induced Shift of ^{13}C=O-NMR Signals[**]

By *Horst Kessler* and *Michael Molter*[*]

In principle, the application of lanthanoid shift reagents (LSR) permits NMR spectroscopic determination of the geometry of molecules in solution. Requirements for such a determination are:

a) Separation of the dipolar contribution (pseudocontact contribution, Δ_{dip}) from the contact contribution (Δ_{con}) and from the diamagnetic contribution (Δ_{dia}) of the observed induced shift (Δ_{obs}).

b) Axial symmetry of the complex and a knowledge of its molecular composition.

c) Knowledge of the site of complexation and the position of the principal magnetic axis.

d) Knowledge of the effect of complexation on the conformational equilibrium of flexible molecules.

Having already considered point d) in a previous study[1] we now examine point a) in the present communication.

The information gained from ^1H-NMR measurements on organic molecules with LSR frequently proves to be insufficient for an unambiguous determination of the requirements listed above. ^{13}C-NMR LSR studies provide additional data. Although LSR have occasionally been employed in assignments of ^{13}C signals, quantitative data have rarely been reported[2-4]. We studied the dependence of the contact contribution Δ_{con} (which is more important for carbons than for protons[5]) of the carbonyl carbons in the compounds *(1)*—*(7)* with Ln(fod)$_3$ (Ln = La, Eu, Pr, Yb; see Table 1; fod = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate).

Table 1. Observed LSR-induced shift Δ_{obs} of the carbonyl carbon atoms in the compounds *(1)*—*(7)*. The molar ratios substrate: LSR = 20:1 and 10:1 were chosen for the ^{13}C-NMR measurements and the values (in ppm) extrapolated linearly to substrate: LSR = 1:1. The error in the Δ_{obs} values is taken as 1.5 ppm due to the use of a 4K memory NMR computer.

R^1—CO—R^2 *(1)*-*(7)*

	$-R^1$	$-R^2$	Δ^{La}_{obs}	Δ^{Eu}_{obs}	Δ^{Pr}_{obs}	Δ^{Yb}_{obs}
(1)	$-CH_3$	$-CH_3$	+16.4	+41.0	−55.3	+149.0
(2)	$-OC_2H_5$	$-CH_3$	+12.0	+ 8.7	−50.4	+131.9
(3)	$-OCH_3$	$-OCH_3$	+ 4.2	0	−51.1	+110.2
(4)	$-N(CH_3)_2$	$-OCH_3$	+ 2.3	−34.8	−36.5	+115.0
(5)	$-N(CH_3)_2$	$-N(CH_3)_2$	− 1.5	−60.2	− 7.1	+ 78.0
(6)	$H_3CN-(CH_2)_3-NCH_3$		0	−78.8	+ 8.8	+ 61.0
(7)	$-N(CH_3)_2$	$-CH_3$	− 5.3	−35.1	−19.0	+108.7

The observed shifts Δ_{obs} consist of a diamagnetic (complexation shift, Δ_{dia}) and a paramagnetic term ($\Delta_{dip} + \Delta_{con}$):

$$\Delta_{obs} = \Delta_{dia} + (\Delta_{dip} + \Delta_{con})$$

The diamagnetic term ($\Delta_{dia} = \Delta^{La}_{obs}$), which was determined by measurements with La(fod)$_3$, decreases with increasing donor strength of the substituents in the series *(1)*—*(6)*[6]. This behavior is in accordance with observations on the protonation of carbonyl compounds[7].

The "anomalous" upfield shifts of the ^{13}CO signals in the amide *(7)*, the urethan *(4)*, and the ureas *(5)* and *(6)* after addition of Eu(fod)$_3$ are particularly interesting. This effect, which has been occasionally mentioned[8], can be utilized in the assignment of ^{13}C-NMR signals[9].

The contribution of Δ_{dip} and Δ_{con} can be obtained from the values listed in Table 1. The ratios of Δ_{con} and Δ_{dip} among the different lanthanoids (Eu^{3+}, Pr^{3+}, and Yb^{3+}) can be assumed constant[10] and provide the remaining equations necessary for separation of Δ_{dip} and Δ_{con}. Use of three different paramagnetic ions provides more data than necessary to check the accuracy of this procedure.

The agreement of Δ_{dip} and Δ_{con} as calculated from the experimental shifts Δ^{Eu}_{obs}, Δ^{Pr}_{obs}, and Δ^{Yb}_{obs} was only moderately good when the theoretical values of *Reuben*[10] and *Dobson et al.*[11] were used; it improved, however, when the experimental values of *Dobson et al.*[11] were employed (Fig. 1).

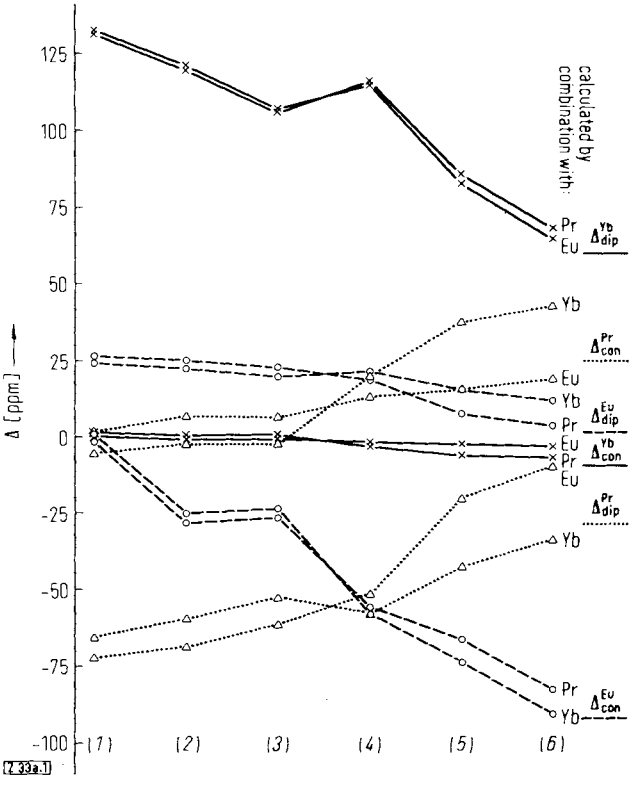


Fig. 1. Contact (Δ_{con}) and pseudocontact shifts (Δ_{dip}) of the carbonyl carbon atoms in *(1)*-*(6)*. The following experimentally determined ratios [11] were used for the separation of the paramagnetic term of the LSR-induced shift ($\Delta_{para} = \Delta_{con} + \Delta_{dip}$):

$\Delta^{Eu}_{dip} : \Delta^{Pr}_{dip} : \Delta^{Yb}_{dip} = (4) : (-11) : (22)$ and

$\Delta^{Eu}_{con} : \Delta^{Pr}_{con} : \Delta^{Yb}_{con} = (-48.1) : (11) : (-1.8)$.

Numerical example:

$\Delta^{Eu}_{para} = \Delta^{Eu}_{con} + \Delta^{Eu}_{dip}$

$\Delta^{Yb}_{para} = \Delta^{Yb}_{con} + \Delta^{Yb}_{dip}$

$\frac{\Delta^{Eu}_{con}}{\Delta^{Yb}_{con}} = \frac{-48.1}{-1.8}$; $\frac{\Delta^{Eu}_{dip}}{\Delta^{Yb}_{dip}} = \frac{4}{22}$

The contribution of the contact term increases rapidly with increasing donor properties of the substituents [*(1)*→*(6)*] and the dipolar term decreases. The increasing basicity of the carbonyl oxygen in the series *(1)*—*(6)*[12] apparently enhances spin delocalization (causing an increase in Δ_{con}) as a result of stronger complexation. The decreasing contribution

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of the dipolar shift could be rationalized because the spin delocalization causes a decrease in the magnetic field.

The above results support the previous suggestion[10] that the pseudocontact term Δ_{dip} for carbon, which is important for conformational studies, is best determined with Yb(fod)$_3$, whereas Eu(fod)$_3$ is more suitable for measurements in which the contact term is important[9].

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[1] *H. Kessler* and *M. Molter*, Angew. Chem. 85, 1059 (1973); Angew. Chem. internat. Edit. 12, 1011 (1973).

[2] *G. E. Hawkes, C. Murzin, D. Leibfritz, S. R. Johns, K. Herwig, R. A. Cooper, D. W. Roberts*, and *J. D. Roberts* in *R. E. Sievers*: NMR Shift Reagents. Academic Press, New York 1973.

[3] *M. Hirayama* and *Y. Hanyu*, Bull. Chem. Soc. Jap. 46, 2687 (1973).

[4] *D. J. Chadwick* and *D. H. Williams*, J. C. S. Chem. Comm. 1974, 128.

[5] *J. Reuben*, Progr. NMR-Spectrosc. 9, 1 (1973).

[6] The donor strength of the substituents of *(6)* is greater than for *(5)*; cf. *H. O. Kalinowski, H. Kessler*, and *A. Walter*, Tetrahedron, 30, 1137 (1974).

[7] *H. O. Kalinowski* and *H. Kessler*, Org. Magn. Res., 6, 305 (1974).

[8] *E. Wenkert, D. W. Cochran, E. W. Hagaman, R. B. Lewis*, and *F. M. Schell*, J. Amer. Chem. Soc. 93, 6271 (1971).

[9] *H. Kessler* and *M. Molter*, Angew. Chem. 86, 553 (1974); Angew. Chem. internat. Edit. 13, 538 (1974).

[10] *J. Reuben*, J. Magn. Res. 11, 103 (1973).

[11] *C. M. Dobson, R. J. P. Williams*, and *A. V. Xavier*, J. C. S. Dalton 1973, 2662.

[12] Measurements on dimethylacetamide *(7)* afford values which, while reflecting the correct general trend, show poorer quantitative agreement.

Use of the Eu(fod)$_3$-Induced Shift for Determination of the Complexation Site and for Signal Assignment in the ^{13}C-NMR Spectra of Protected Dipeptides[**]

By *Horst Kessler* and *Michael Molter*[*]

Assignment of the signals of the carbonyl carbon atoms in ^{13}C-NMR spectra of peptides frequently proves impossible by conventional methods. In certain cases the use of Eu(fod)$_3$ (tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)-europium) as a shift reagent is useful. With this reagent the contact contribution Δ_{con} is so large that it overcompensates the pseudocontact term Δ_{dip} in the case of urethans, amides, and ureas and leads to an "anomalous" upfield shift of the ^{13}C=O signal[1,2].

In the carbonyl region of its ^{13}C-NMR spectrum a Z- or boc-dipeptide methyl ester shows three signals. The urethan carbonyl carbon peak at 154–156 ppm is distinctly separated from those of the amide and ester carbonyl carbons (169–173 ppm). Only one of the latter signals is shifted upfield after the addition of Eu(fod)$_3$. Upfield shifts of ester carbonyl carbons cannot be observed, whereas such shifts do occur with amide carbonyl carbons due to the large contact term[11]. This allows the assignment of these two signals (Table 1). There are only two carbonyl groups which can complex with the shift reagent in boc-Gly-OCH$_3$. The urethan carbonyl group ($\delta = 156.0$ ppm) shows the above-mentioned "anomalous" upfield shift ($\Delta_{obs} = -9$ ppm[3]), which indicates a considerable degree of complexation. In the protected dipeptides

Table 1. ^{13}C-NMR shifts of dipeptides. The values are given in ppm relative to TMS (solvent CDCl$_3$). The values given in parentheses are the Eu(fod)$_3$-induced shifts (extrapolated to Eu(fod)$_3$:substrate = 1:1). [a] Remaining aromatic signals of Z-Phe-Ala-OCH$_3$: 130.0, 128.7; 128.3; 127.1.

	Urethan CO	Amide CO	Ester CO
Range of chemical shift [ppm]	154–156	169–173	169–173
Model compounds	$(H_3C)_2N$, H_3CO, C=O; 157.1 (−35.0)	$(H_3C)_2N$, H_3C, C=O; 170.7 (−35.0)	H_5C_2O, H_3C, C=O; 170.9 (+9.0)

Z-Phe-Ala-OCH$_3$: [a] 136.0; 136.4; CH_2 38.5; CH_3 17.7; CH_2 66.7; 156.0 (+2.6); 55.8 171.2 (−24.1); 47.8 173.0 52.4 (+5.4)

Boc-Phe-Phe-OCH$_3$: 126.5; 128.0; 128.8; 126.5; 136.3; 135.4; CH_2 38.2; CH_2 37.8; $(CH_3)_3C$ 28.1; 76.6 154.7 (+1.7); 55.7 170.9 (−20.7); 53.2 170.5 51.9 (+9.4)

Boc-Gly-Phe-OCH$_3$: 127.0; 128.4; 129.1; 135.8; CH_2 37.8; $(CH_3)_3C$ 28.2; 79.9 156.0 (−1.8); 44.2 169.5 (−11.8); 53.1 171.8 52.1 (+3.7)

Boc-Phe-Gly-OCH$_3$: 126.7; 128.4; 129.3; 137.0; CH_2 38.6; $(CH_3)_3C$ 28.3; 80.1 155.6 (−2.6); 55.8 172.2 (−22.1); 41.2 170.0 52.1 (+3.9)

Boc-Gly-Gly-OCH$_3$: $(CH_3)_3C$ 28.2; 80.0 155.6 (−1.7); 44.1 169.6 (−15.2); 41.0 169.6 52.2 (+3.4)

Trt-Gly-Gly-OCH$_3$: 126.7; 128.0; 128.4; 145.2; 71.1; 52.3 171.8 (−27.3); 40.8 170.3 52.3 (+6.5)

(Table 1) the upfield shift of the urethan CO signal is small compared to that of the amide signal, thus indicating preferred complexation at the amide carbonyl group. However, the weak upfield shift of the urethan CO signal in boc-Phe-Gly-OCH$_3$, boc-Gly-Phe-OCH$_3$, and boc-Gly-Gly-OCH$_3$ demonstrates that this group is partially complexed too[5].

This indicates that in protected dipeptides several complexing sites compete for the lanthanoid shift reagents. Hence their use in conformational analysis of such compounds[6] becomes

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problematic if no information is available concerning the relative complexation constants. The presence of compounds whose conformational equilibria are affected by complexation can also interfere with structural determinations[4].

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[1] *H. Kessler* and *M. Molter*, Angew. Chem. 86, 552 (1974); Angew. Chem. internat. Edit. 13, 537 (1974).

[2] *E. Wenkert, D. W. Cochran, E. W. Hagaman, R. B. Lewis*, and *F. M. Schell*, J. Amer. Chem. Soc. 93, 6271 (1971).

[3] The measurements were performed at 100 C. At this temperature the exchange between the *Z,E* isomers is frequent. At 0 C (slow exchange) a nonlinear behavior of the lanthanoid-induced shift is found with preferential complexation of the *E* form, as observed in the ^{1}H-NMR spectra[4].

[4] *H. Kessler* and *M. Molter*, Angew. Chem. 85, 1059 (1973); Angew. Chem. internat. Edit. 12, 1011 (1973).

[5] The positive shift of this signal with Yb(fod)$_3$ shows that the upfield shift is not caused by the angle term in the geometrical factor of the dipolar contribution (pseudocontact term) but by the contact term.

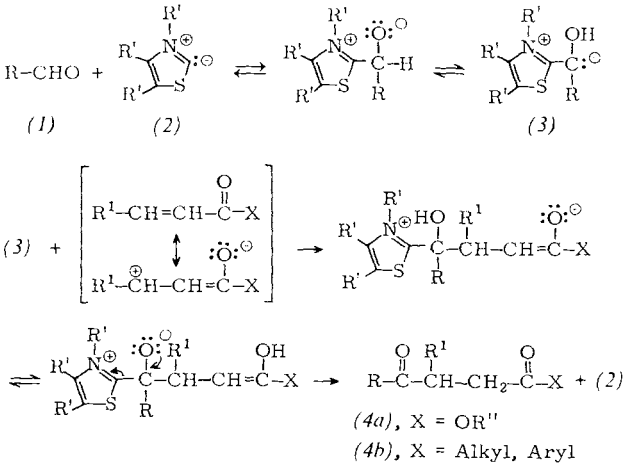
[6] *L. C. Martinelli, J. L. Honigberg*, and *L. A. Sternson*, Tetrahedron 29, 1671 (1973).

Addition of Aliphatic Aldehydes to Activated Double Bonds[1]

By *Hermann Stetter* and *Heinrich Kuhlmann*[*]

Aromatic and heterocyclic aldehydes can be added to α,β-unsaturated nitriles, esters and ketones under catalytic influence of cyanide ions. Aliphatic aldehydes, however, do not add under these conditions because of the strong basicity of the cyanides.

We have found that both aromatic and heterocyclic aldehydes as well as aliphatic aldehydes *(1)* can be added to α,β-unsaturated nitriles, esters, and ketones when thiazolium salts, whose catalytic activity in the formation of acyloins is well known[2], are employed in the presence of bases. γ-Ketonitriles, γ-ketoesters *(4a)*, and γ-diketones *(4b)*, respectively, are formed. The reaction course differs from that mentioned earlier[3] only in the mode of formation of the intermediary carbanion *(3)*.



The reaction can be carried out in polar solvents, *e.g.* alcohols, dimethylformamide, water, and corresponding mixtures. In the case of the examples listed in Table 1, the following reaction conditions were used:

Table 1. Examples for the reaction of aldehydes with α,β-unsaturated carbonyl compounds or nitriles.

R–CHO + R^1–CH=CH–R^2 → R–CO–CHR^1–CH$_2$–R^2

R	R^1	R^2	Yield [%]	B.p. [°C/torr] m.p. [°C]	Ref.
CH_3	H	$COCH_3$	50	185–192/760 [a]	[4]
CH_3	H	C≡N	30	100–103/12 [b]	[6]
n-C_3H_7	H	$COCH_3$	62	45–48/0.2	
n-C_3H_7	C_6H_5	COC_6H_5	60	158–164/0.2	
n-C_3H_7	C_6H_5	$COCH_3$	40	95–100/0.2	
α-Furyl	H	C≡N	60	104–105/0.35 77–78	[8]
α-Furyl	H	$COOC_2H_5$	38	115–120/0.5 52–53	[8]
C_6H_5	C_6H_5	COC_6H_5	75	124–126	[9]

[a] Dioxime: m.p. = 134–135 °C [5].
[b] 4-Nitrophenylhydrazone: m.p. = 178–179 °C [7].

A solution of the aldehyde *(1)* (1 mol), thiazolium salt (*e.g.* 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride or 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide) (*ca.* 0.1 mol), triethylamine or similar bases (0.2 mol), and the α,β-unsaturated compound (1 mol) in methanol, ethanol, dimethylformamide or mixtures thereof or water (1500 ml) is heated for 24 h under nitrogen at *ca.* 60–70 °C. The solvent is then removed by distillation and the reaction product worked up by fractional distillation or recrystallization.

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[1] Addition of Aldehydes to Activated Double Bonds, Part 5. Part 4: *H. Stetter* and *M. Schreckenberg*, Chem. Ber. 107 (1974), in press.

[2] *R. Breslow*, J. Amer. Chem. Soc. 80, 3719 (1958); *U. Tagaki* and *H. Hara*, J. C. S. Chem. Comm. 1973, 891.

[3] *H. Stetter* and *M. Schreckenberg*, Angew. Chem. 85, 89 (1973); Angew. Chem. internat. Edit. 12, 84 (1973).

[4] *K. W. F. Kohlrausch* and *A. Pongartz*, Ber. Deut. Chem. Ges. 66, 1355 (1933).

[5] *C. Paal*, Ber. Deut. Chem. Ges. 18, 59 (1885).

[6] *G. B. Buckley, T. J. Elliott, F. G. Hunt*, and *A. Lowe*, J. Chem. Soc. 1947, 1505.

[7] *E. O. Leupold* and *H. Vollmann*, DRP 691 621 (1940); I.G. Farbenindustrie.

[8] *E. B. Knott*, J. Chem. Soc. 1947, 1190.

[9] *A. Smith*, J. Chem. Soc. 57, 645 (1890).

Crystal and Molecular Structure of *cis*-Trioxatris-σ-homobenzene (*cis*-"Benzene Trioxide")[**]

By *Walter Littke* and *Ulrich Drück*[*]

The chemistry of carbo- and heterocyclic *cis*-tris-σ-homobenzene compounds raises questions whose answers require a knowledge of exact structural parameters. In the present communication we report the results obtained in an X-ray structure analysis of *cis*-trioxatris-σ-homobenzene[1, 2].

The compound forms orthorhombic crystals from solutions in methanol or acetone. The unit cell, having the dimensions $a = 9.169 \pm 0.004$, $b = 10.325 \pm 0.006$, $c = 10.892 \pm 0.006$ Å, contains eight molecules and belongs to the space group Pbca. The experimentally determined ($d_{exp} = 1.62$ g/cm^3) and calculated density ($d_{calc} = 1.61$ g/cm^3) are in good agreement. This density value, which is relatively high for an organic substance

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containing no heavy atoms, is attributable to dense packing within the cell.

A single crystal ground to a sphere (0.7 mm diam.) was mounted on a computer-controlled four-circle diffractometer (CAD 4, Enraf-Nonius) and 1319 symmetry-independent reflections

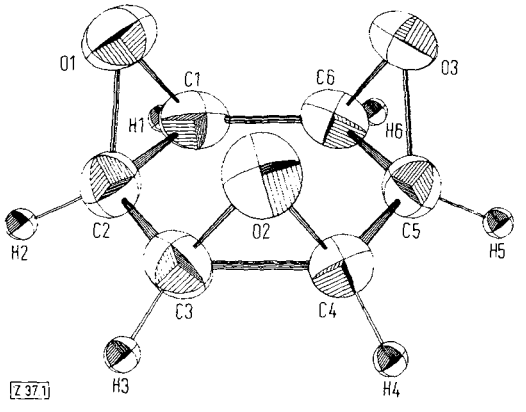


Fig. 1. *cis*-"Benzene trioxide" molecule, computer plot.

were measured with $Mo_{K\gamma}$ radiation. The positional parameters of all the atoms except the hydrogens could be determined by use of the symbolic addition method[3] and subjected to least-squares anisotropic refinement. The hydrogen atoms could then all be localized by Fourier difference synthesis, and further sharpening of all atomic parameters (anisotropic for C and O, isotropic for H) finally led to an R value of 0.056.

Figure 1 shows the highly symmetrical structure of *cis*-"benzene trioxide". The six carbons (cyclohexane ring) are coplanar (maximum deviation ±0.01 Å). Further planes can be constructed 0.42 Å below this ring plane through the six hydrogens (maximum deviation ±0.06 Å) and 1.19 Å above the ring plane through the three oxygens. All three planes are parallel. The three oxirane rings are twisted outwards from the C_6 ring (dihedral angle = 106.9°). The oxygen atoms are located at the apices of an almost equilateral triangle having the edge lengths O1—O2 = 2.86, O2—O3 = 2.80, and O3—O1 = 2.81 Å. These distances very closely resemble normal oxygen contacts (van der Waals radius 1.40 Å); it may therefore be presumed that similar conditions also apply for the two neighboring oxygens in *trans*-"benzene trioxide".

The most important intramolecular distances and bond angles of the molecule are shown schematically in Figure 2.

The carbon atoms bridged by oxygen have slightly shorter bonding distances (average 1.470 Å) than the unbridged ones (mean value 1.487 Å). Overall, the C—C bond lengths (mean value for all six bonds 1.479 Å) correspond to an sp^2—sp^2 single bond (1.48 Å). The mean value of the six CCH angles directed away from the oxirane rings (C6—C1—H1, H2—C2—C3, C2—C3—H3, H4—C4—C5, C4—C5—H5, and H6—C6—C1) amounts to 116.50 .

Table 1. Structural data of ethylene oxide (gaseous, microwave spectroscopy) [4] and *cis*-"benzene trioxide".

Ethylene oxide		Benzene trioxide	
Distances	[Å]	Distances (mean values)	[Å]
C—H	1.082	C—H	0.985
C—C	1.472	C—C (oxirane ring)	1.470
C—O	1.436	C—O	1.437
Angles	[°]	Angles (mean values)	[°]
H—C—H	116.68	C—C—H	116.50
C—O—C	61.40	C—O—C	61.52

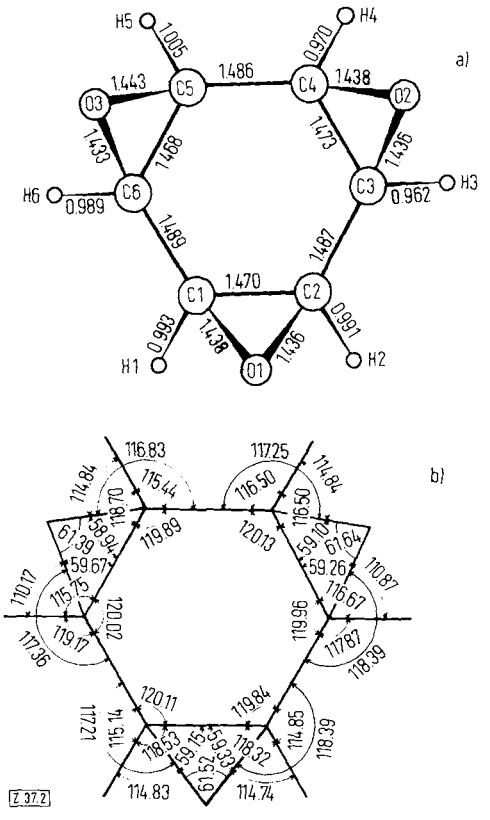


Fig. 2. Molecular geometry of *cis*-"benzene trioxide": a) bond lengths [Å]; b) bond angles [ ].

The extent of agreement of the corresponding structural parameters of *cis*-"benzene trioxide" and ethylene oxide—except for the C—H bond lengths—is remarkable (Table 1). Thus the *cis* arrangement of the three oxirane rings in *cis*-"benzene trioxide" which is favorable for conjugative interaction is without consequence in this respect. Accordingly, good agreement is observed with the values published by *Kitahara et al.*[5] for 9-cyano-*trans*-dioxatris-σ-homobenzene.

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[1] *R. Schwesinger* and *H. Prinzbach*, Angew. Chem. 85, 1107 (1973); Angew. Chem. internat. Edit. 12, 989 (1973); X-ray structure analysis of *cis*-triazatris-σ-homobenzene (*cis*-"benzene triimine") has likewise also been completed (*W. Littke* and *U. Drück*, to be published).

[2] *R. Schwesinger* and *H. Prinzbach*, Angew. Chem. 84, 990 (1972); Angew. Chem. internat. Edit. 11, 942 (1972); *E. Vogel, H.-J. Altenbach*, and *C.-D. Sommerfeld*, ibid. 84, 986 (1972); and 11, 939 (1972), resp.

[3] *J. Karle* and *I. L. Karle*, Acta Crystallogr. 21, 849 (1966).

[4] *W. Gordy* in *W. West*: Chemical Applications of Spectroscopy. Wiley-Interscience, New York 1956, p. 92.

[5] *C. Kabuto, M. Yagihara, T. Asao*, and *Y. Kitahara*, Angew. Chem. 85, 860 (1973); Angew. Chem. internat. Edit. 12, 836 (1973).

Isomerization by Ring Expansion in Silylated Phosphorus Ylides[1]

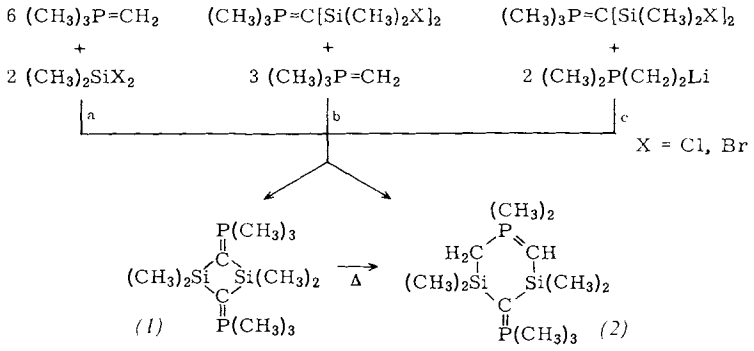
By *Wolfgang Malisch* and *Hubert Schmidbaur*[*]

On reaction of alkylidenetrialkylphosphoranes with dialkyldihalosilanes[2], ylidic derivatives of 1,3-disilacyclobutanes of

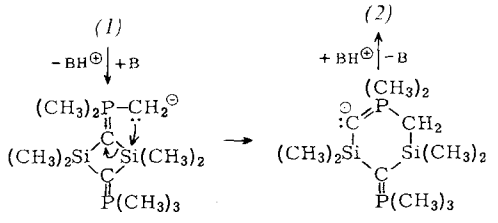
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type *(1)* are formed surprisingly readily; their cyclobutane analogs are incapable of existence[3]. It appears that two Si atoms, but not two C atoms, provide sufficient shielding between the two carbanionic centers of the ylide functions[4].

By variation of the reaction conditions and the substituents we have now found, however, that *(1)* is not the thermodynamically most stable product but merely a kinetically favored initial intermediate of such reactions: on prolonged reaction and in the presence of a slight excess of ylide (path a, b) or metalated ylide (path c) as a base the isomeric six-membered cyclic compound *(2)* is formed irreversibly. Moreover, *(1)* also transforms to compound *(2)* slowly at 25 °C, and more rapidly at 120 °C. The process corresponds to a ring expansion involving a formerly exocyclic ylide function.

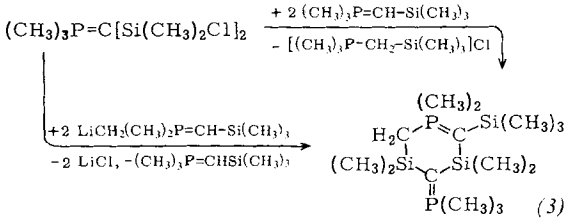


The isomerization process *(1)* → *(2)* is induced by deprotonation of *(1)* at a PCH_3 group and nucleophilic attack of the resulting carbanion at a silicon atom. Ring opening generates a new carbanion which yields the CH group of *(2)* by concerted abstraction of a proton.



Silacyclobutane ring opening by ylides proceeds similarly[5]. Earlier results obtained on the isomerization of five- and six-membered *disilanyl* ylide ring systems[6] are confirmed and supplemented by this new variant of carbanionic rearrangement[7].

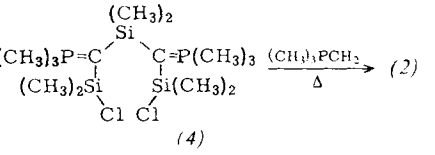
A derivative *(3)* which is substituted on the ylidic C atom of ring *(2)* is formed quantitatively on reaction of bis-(dimethylchlorosilyl)methylenetrimethylphosphorane[2] with trimethylsilylmethylenetrimethylphosphorane[8] or its metalation product[4]. Silylation of the starting ylide prevents formation of a four-membered ring in this case.



The composition of *(2)* (m.p. 32—34 °C, b.p. 113—115 °C/0.1 torr) and *(3)* (m.p. 65—67 °C, b.p. 119—121 °C/0.01 torr) was established by elemental analysis and molecular weight determination. The structure follows from the NMR spectra.

^{1}H-NMR (C_6H_6, TMS int., 35 °C): *(2)*: τ$(CH_3)_3$P 8.92 ppm (d, 9H), *J*(HCP) 11.9 Hz; τ$(CH_3)_2$P 8.88 (d, 6H), *J*(HCP) 11.8; τCH_2 9.22 (dd, 2H), *J*(HCP) 15.0; τCH_3Si 9.59 (d, 6H), *J*(HCSiCP) 0.8; τCH_3Si' 9.72 (s, 6H); τCH 10.40 (ddt[9], 1H).—*(3)*: τ$(CH_3)_3$P 8.90 (d, 9H), *J*(HCP) 11.9; τ$(CH_3)_2$P 8.74 (d, 6H), *J*(HCP) 11.75; τCH_2 9.05 (d, 2H), *J*(HCP) 14.75; τ$(CH_3)_2$Si 9.81 (dd, 6H), *J*(HCSiCP) 0.4, *J*(HCSiCP') 0.3; τ$(CH_3)_2$Si' 9.68 (dd, 6H), *J*(HCSiCP) 0.4, *J*(HCSiCP') 0.8; τ$(CH_3)_3$Si 9.71 (s, 9H).

^{31}P-NMR (C_6H_6, 85% H_3PO_4, 35 °C): *(2)*: δP +1.525 ppm, δP' +1.274, AB, *J*(PP') 6.4 Hz.—*(3)*: δP +2.39, δP' −2.86, AX, *J*(PP') 3.8 (^{1}H-decoupled).



On reaction with $(CH_3)_2SiCl_2$ at −78 °C compound *(1)* undergoes ring cleavage to give *(4)*, m.p. 88—89 °C[10]. Attempted ring closure with $(CH_3)_3P{=}CH_2$ leads to ylide intermediates of higher molecular weight, and presumably also to larger rings. However, distillation again affords *(2)*, which appears to be especially stable.

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[1] Organosilicon Chemistry of Phosphorus Ylides, Part 19. Part 18: *H. Schmidbaur* and *H. Stühler*, Angew. Chem. 85, 345 (1973); Angew. Chem. internat. Edit. 12, 321 (1973).

[2] *H. Schmidbaur* and *W. Malisch*, Angew. Chem. 82, 84 (1970); Angew. Chem. internat. Edit. 9, 77 (1970); Chem. Ber. 103, 97 (1970).

[3] *H. J. Bestmann* and *R. Zimmermann* in *G. M. Kosolapoff* and *L. Maier*: Organic Phosphorus Compounds, Vol. 3, pp. 1–185. Wiley-Interscience, New York 1972.

[4] *H. Schmidbaur* and *W. Malisch*, Chem. Ber. 103, 3007, 3448 (1970); 104, 150 (1971).

[5] *H. Schmidbaur* and *W. Wolf*, Angew. Chem. 85, 344 (1973); Angew. Chem. internat. Edit. 12, 320 (1973).

[6] *H. Schmidbaur* and *W. Vornberger*, Angew. Chem. 82, 773 (1970); Angew. Chem. internat. Edit. 9, 737 (1970); Chem. Ber. 105, 3173 (1972).

[7] *R. West*, Pure Appl. Chem. 19, 291 (1969).

[8] *H. Schmidbaur* and *W. Tronich*, Chem. Ber. 100, 1032 (1967); and further references cited therein.

[9] Only on first order analysis does τCH approximately represent a double doublet of triplets which simplifies to a 1:2:1 triplet, *J*(HCPCH) 1.25, on P decoupling. Additional couplings from the CH_3 groups and the P-P' interaction lead to broadening of the outer peaks which disappear on partial H decoupling.

[10] ^{1}H-NMR: τCH_3P 9.33 (d, 18H), *J*(HCP) 12; τCH_3SiCl 9.85 (s, 12H); τCH_3Si 10.13 (s, 6H). ^{31}P-NMR: δP −3.16 (^{1}H-decoupled).

The Crystal Structure of a 1:1 Sodium Perchlorate Complex of 1,4-Anhydroerythritol (*cis*-3,4-Tetrahydrofurandiol)

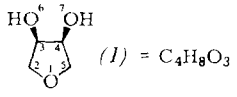
By *R. E. Ballard*, *A. H. Haines*, *E. K. Norris*, and *A. G. Wells*[*]

There is interest in the complexes of alkali and alkaline earth metals with neutral molecules such as macrocyclic polyethers[1], macrocyclic antibiotics[2], and cryptates[3]. We report the formation of new complexes between 1,4-anhydroerythritol (*cis*-3,4-tetrahydrofurandiol) *(1)*[4] and the iodide, thiocyanate, and perchlorate of sodium which are obtained

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as hygroscopic crystals by concentration of equimolar ethanolic solutions of the two components.

After recrystallization from 2-propanol/ethyl acetate the derivatives analyzed as [2(*1*)·NaI], [(*1*)·NaSCN], and [(*1*)·$NaClO_4$].



(*1*) = $C_4H_8O_3$

Crystal data: $C_4H_8O_3 \cdot NaClO_4$. Orthorhombic; $a = 12.77$, $b = 7.28$, $c = 17.69$ Å; $V = 1644.5$ Å^3; $d_{calc} = 1.83$; $d_{exp} = 1.79$; $Z = 8$; space group $P2_12_12_1$.

Intensities of reflections ($Cu_{K\alpha}$ radiation, Ni-filtered) from a crystal of the perchlorate mounted in a Lindemann tube on a Weissenberg camera were measured visually. The coordinates of the sodium and chlorine ions were found by a direct method program[5]. Application of Fourier technique established the structure with the exception of the hydrogen atoms, and refinement gave $R = 0.129$.

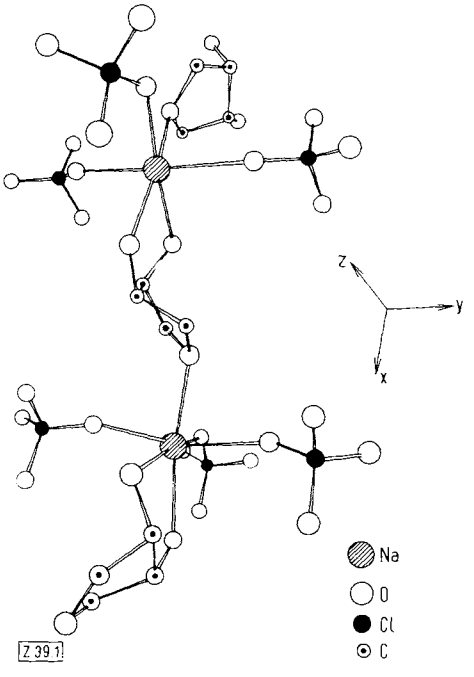


Fig. 1. Perspective section from the crystal structure of the complex [(*1*)·$NaClO_4$].

Figure 1 shows the similar environments of the two types of sodium ion in [(*1*)·$NaClO_4$]. Each is coordinated to six oxygen atoms which lie at the corners of a distorted octahedron. These six atoms comprise three oxygens from three different perchlorate ions, two from the hydroxyl groups of one molecule of (*1*), the remaining one being the tetrahydrofuran oxygen of a second molecule of (*1*). The resulting structure is an infinite network.

Planarity analyses of the two types of tetrahydrofuran ring (see Fig. 1) indicate near envelope conformations. In the one enantiomer C(3) in both rings is displaced 0.57 Å from the least squares plane through the other four atoms; the displacement in both types of ring is to that side from which the numbering (see formula (*1*)) appears anticlockwise. The torsional angles of the rings are listed in Table 1.

Table 1. Torsional angles [ ] in the rings (*1*) in the complex [(*1*)·$NaClO_4$]; standard deviation ≈ 0.8 .

Ring 1		Ring 2	
O(1)—C(2)—C(3)—C(4)	−40.0	O(1')—C(2')—C(3')—C(4')	−40.0
C(2)—C(3)—C(4)—C(5)	35.1	C(2')—C(3')—C(4')—C(5')	33.0
C(3)—C(4)—C(5)—O(1)	−17.7	C(3')—C(4')—C(5')—C(1')	−15.6
C(4)—C(5)—O(1)—C(2)	− 6.5	C(4')—C(5')—O(1')—C(2')	− 9.0
C(5)—O(1)—C(2)—C(3)	28.9	C(5')—O(1')—C(2')—C(3')	30.4
O(6)—C(3)—C(4)—O(7)	41.0	O(6')—C(3')—C(4')—O(7')	40.1

Normal values were found for Na—O separations, which lie in the ranges 2.32—2.59 Å ($OClO_3$), 2.29—2.32 Å (OH), and 2.35—2.36 Å (etheric oxygens). These Na—O distances are smaller than the Na—O (ether) distances found in the complexes of "dibenzo[18]crown-6" with NaBr[6], but similar to those found in the "benzo[15]crown-5"-sodium iodide complex[7].

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[1] *C. J. Pedersen* and *H. K. Frensdorff*, Angew. Chem. *84*, 16 (1972); Angew. Chem. internat. Edit. *11*, 16 (1972).

[2] *M. Pinkerton, L. K. Streinrauf*, and *P. Dawkins*, Biochem. Biophys. Res. Commun. *35*, 512 (1969); *M. Dobler, J. D. Dunitz*, and *J. Krajewski*, J. Mol. Biol. *42*, 603 (1969); *M. Dobler, J. D. Dunitz*, and *B. T. Kilbourn*, Helv. Chim. Acta *52*, 2573 (1969).

[3] *J. M. Lehn* and *J. P. Sauvage*, Chem. Commun. *1971*, 446.

[4] *J. S. Brimacombe, A. B. Foster, M. Stacey*, and *D. H. Whiffen*, Tetrahedron *4*, 351 (1958).

[5] Program by *G. Sheldrick*, University Chemistry Laboratory, Lensfield Road, Cambridge.

[6] *M. A. Bush* and *M. R. Truter*, J. Chem. Soc. *B 1971*, 1440.

[7] *M. A. Bush* and *M. R. Truter*, J. C. S. Perkin II *1972*, 341.

Stabilization of the Pentacoordination of Phosphorus by Tridentate Ligands[**]

By *Dieter Hellwinkel* and *Wolfgang Krapp*[*]

In general the stabilities of derivatives of pentacoordinated phosphorus increase in the following order: acyclic < monocyclic < spirocyclic[1]. Some phosphoranes with tridentate ligands have recently also been reported and some of these have notable stability[2]. A few years ago we began systematic studies with the object of developing tridentate ligand systems that would also constrain phosphoranes to assume unusual geometries[3]. We now report a type of tridentate ligand that is optimally suited to the trigonal-bipyramidal structures preferred by such compounds[4].

For this purpose we first synthesized 1-bromo-2,6-bis(hydroxymethyl)benzene [2-bromo-*m*-phenylenedimethanol] which can, after double etherification with dihydropyran, be converted smoothly into the 1-lithium derivative. Reaction of this derivative with diphenylchlorophosphane afforded diphenyl[2,6-bis(tetrahydro-2-pyranyloxymethyl)phenyl]-phosphane (*1*), which yielded the phosphorane (*4*) even in attempts merely to remove the tetrahydropyranyl protecting groups (THP) by acid transacetalization in boiling ethanol. This is reasonable only if spontaneous atmospheric oxidation of the phosphane (*1*) is assumed to have occurred. In fact the phosphane oxide (*3*) obtainable from the phosphane (*1*)

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by means of H_2O_2 is readily converted into 8,8-diphenyl-2*H*,6*H*-1,2-oxaphospholo[4,3,2-*hi*][2,1]benzoxaphosphole *(4)* by HCl. *(4)* is obtained more simply and directly from *(1)* by reaction with 2 equivalents of bromine. The unprotected hydroxylic phosphane oxide *(2)* that is formed on oxidation of *(1)* by H_2O_2 in acid solution can be transformed almost quantitatively into the phosphorane *(4)* by heating it for a short time at *ca.* 200 °C, in complete accord with the facts that the mass spectrum of *(2)* is dominated by the $(M-18)^+$ fragment and that *(2)* melts with evolution of gas.

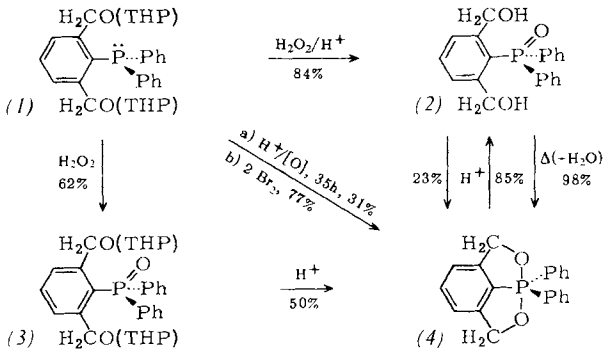


Table 1. Physical properties of the phosphorane *(4)*.

M. p. [°C]	$\delta^{31}P$ [ppm]	$\delta(H_2COP)$	$^3J(H_2COP)$ [Hz]	$^4J(H_2CCCH)$	ν(P—O) [cm^{-1}]	MS *m/e*, *I*
131.4	+22.9	5.02	2.8	0.6	1025 1045	320, 88% 319, 100%

To our knowledge, this is the first case in which a (tetrahedral) triarylphosphane oxide has been "acetalized" by simple loss of water to a (trigonal-bipyramidal) dialkoxytriarylphosphorane[5]. Our studies have also revealed the astonishing thermal stability of the phosphorane *(4)*: the compound survives heating for several hours above 200 °C and sublimes without decomposition even under atmospheric pressure. This unusual stability accords with theoretical views on the possible modes of fragmentation of derivatives of pentacoordinated phosphorus[6]: according to orbital-symmetry considerations only axial-axial and equatorial-equatorial fragmentations (or rearrangements) are thermally allowed[7]; in the case of *(4)*, however, both processes would lead to thermodynamically unfavorable products, namely to an enormously strained peroxide[8] or to a cyclic phosphonous ester with "T"-geometry in addition to biphenyl.

The ligand system that has been so successful in stabilizing the coordination number 5 for phosphorus could also be useful for preparation of hypervalent[9] species of other main-group elements.

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[1] Cf.: *D. Hellwinkel* in *G. M. Kosolapoff* and *L. Maier*: Organic Phosphorus Compounds, Vol. 3. Wiley, New York 1972, p. 185.

[2] *D. D. Swank, C. N. Caughlan, F. Ramirez*, and *J. F. Pilot*, J. Amer. Chem. Soc. *93*, 5236 (1971); *D. Houalla, J. F. Brazier, M. Sanchez*, and *R. Wolf*, Tetrahedron Lett. *1972*, 2969; *E. Duff, S. Trippett*, and *P. J. Whittle*, J. C. S. Perkin I *1973*, 972; *W. C. Hamilton, J. S. Ricci, F. Ramirez, L. Kramer*, and *P. Stern*, J. Amer. Chem. Soc. *95*, 6335 (1973).

[3] *D. Hellwinkel* and *W. Schenk*, Angew. Chem. *81*, 1049 (1969); Angew. Chem. internat. Edit. *8*, 987 (1969).

[4] Cf.: *R. Luckenbach*: Dynamic Stereochemistry of Pentacoordinated Phosphorus Compounds and Related Elements. Thieme-Verlag, Stuttgart 1973.

[5] *A. Schmidpeter* has meanwhile reported similar observations in a personal communication to us.

[6] *W. Krapp*, Diplomarbeit, Universität Heidelberg 1974.

[7] *R. Hoffmann, J. M. Howell*, and *E. L. Muetterties*, J. Amer. Chem. Soc. *94*, 3047 (1972).

[8] Peroxides in turn react readily with phosphanes to give dioxyphosphoranes: *D. B. Denney, D. Z. Denney, B. C. Chang*, and *K. L. Marsi*, J. Amer. Chem. Soc. *91*, 5243 (1969).

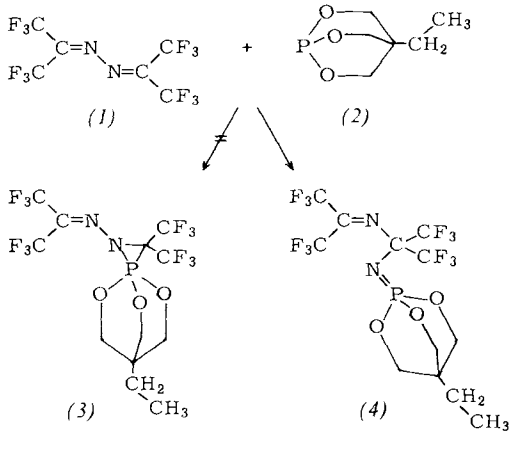
[9] *J. I. Musher*, Angew. Chem. *81*, 68 (1969); Angew. Chem. internat. Edit. *8*, 54 (1969).

Structure of the 1:1-Adduct of Hexafluoroacetone Azine and 4-Ethyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane

By *Alfred Gieren* and *Poojappan Narayanan*[*], together with *Klaus Burger* and *Willy Thenn*[**]

1,2λ^5-Azaphosphiridine structures *(3)* were recently proposed for the 1:1-adducts formed on reaction of hexafluoroacetone azine *(1)* with phosphites and with tris(dimethylamino)phosphane[1]. An X-ray structure analysis of the 1:1-adduct obtained by the same process from *(1)* and 4-ethyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane *(2)*[2] shows the structure of a 4-ethyl-1-[5,5,5-trifluoro-2,2,4-tris(trifluoromethyl)-1,3-diaza-3-pentenylidene]-2,6,7-trioxa-1λ^5-phosphabicyclo-[2.2.2]octane *(4)*. The previous compounds[1] are therefore not azaphosphiridines *(3)* but iminophosphoranes of type *(4)*.

The structure analysis was carried out with orthorhombic single crystals of *(4)* obtained from hexane solution: space group $Pna2_1$ or Pnam; $a = 12.19_8$, $b = 15.34_8$, $c = 10.00_0$ Å;



$d_{obs} = 1.71$, $d_{calc} = 1.73\ g \cdot cm^{-3}$; $Z = 4$ (one or half a molecule per asymmetric unit). It is difficult to distinguish between $Pna2_1$ (acentric) and Pnam (centrosymmetric) (see below) because the molecule contains a mirror or pseudomirror plane, whose orientation coincides with the crystallographic mirror

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plane in Pnam. 1696 independent reflections were measured with $Cu_{K\alpha}$-radiation up to a Θ value of 65° on an automatic single-crystal diffractometer; two crystals were used for these measurements because the substance decomposed. The intensities of 868 reflections lay below the significance limit ($I \leqslant 2\sigma_I$), which indicates an unusually high temperature factor (mean value for all atoms 15 Å^2) or disorder of molecules in the crystal.

Since the *E*-value statistics indicated an acentric space group we first assumed the space group $Pna2_1$. The structure was solved by direct methods by using the PHASDT program[3]. The solution with the best consistency gave phases for 211 reflections. An *E*-Fourier synthesis calculated therefrom showed the positions of all the atoms (other than H) except the terminal carbon of the C_2H_5 group. This C atom (temperature factor 19 Å^2) was only localized after introduction of anisotropic temperature factors at $R = 14.0\%$ in a difference Fourier synthesis. On refinement by the method of least squares (ORFLS program)[4] the strong parameter correlations caused by the pseudomirror plane led to convergence difficulties, but these were overcome on use of isotropic temperature factors first by alternate refinement of the scaling factor on the one hand and of the remaining parameters on the other and then by splitting into three overlapping partial cycles. Owing to the large number of parameters, the refinement with anisotropic temperature factors was carried out in cycles made up of two overlapping partial cycles. In that work a shift limitation (0.6) proved useful. The *R* factor amounts to 9.0% (observed reflections).

In parallel work the structure was also refined for the centrosymmetric space group Pnam. Here convergence set in at $R = 12.6\%$. The Hamilton test[5] indicated relevance of the *R*-factor difference on refinement in the alternative space groups and thus favored $Pna2_1$. The calculated difference Fourier syntheses for the two space groups and comparison of the temperature factors also favored this space group.

Figure 1 shows the molecular structure after refinement in $Pna2_1$. The significance of the bond lengths suffices for distinction between single and double bonds, but the dispersion of atomic distances and bond angles does not justify detailed discussion, which will therefore not be undertaken here.

The preference for the acentric space group indicates a somewhat staggered conformation for the 2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane system. However, even if the centrosymmetric space group is assumed the staggered conformation is more probable (statistical disorder?) than a fully eclipsed conformation which was published for the same system in $OP(OCH_2)_3CCH_3$[6]. The two conformations were also found for the bicyclo[2.2.2]octane system[7].

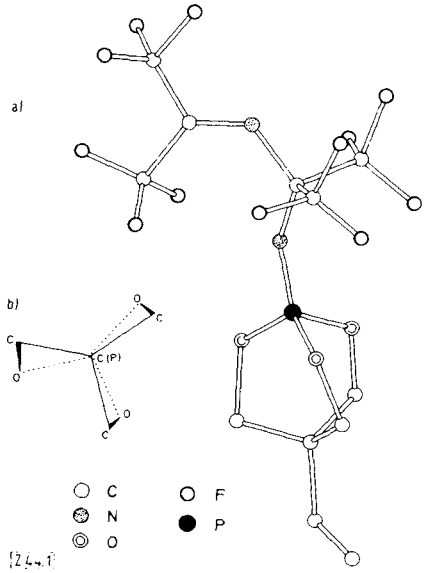


Fig. 1. a) Molecular structure of 4-ethyl-1-[5,5,5-trifluoro-2,2,4-tris(trifluoromethyl-1,3-diaza-3-pentenylidene]-2,6,7-trioxa-1λ^5-phosphabicyclo[2.2.2]-octane (4). b) Conformation of the 2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane system.

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[1] *K. Burger, J. Fehn*, and *W. Thenn*, Angew. Chem. 85, 542 (1973); Angew. Chem. internat. Edit. 12, 502 (1973).

[2] *K. Burger, W. Thenn, J. Fehn*, and *A. Gieren*, Chem. Ber. 107, 1526 (1974).

[3] *W. Hoppe, J. Gassmann*, and *K. Zechmeister* in *F. R. Ahmed*: Crystallographic Computing. Munksgaard, Copenhagen 1970, p. 26.

[4] *J. M. Stewart*: X-Ray 67 Program System for X-ray Crystallography. Computer Science Centre, University of Maryland.

[5] *W. C. Hamilton*, Acta Crystallogr. 18, 502 (1965).

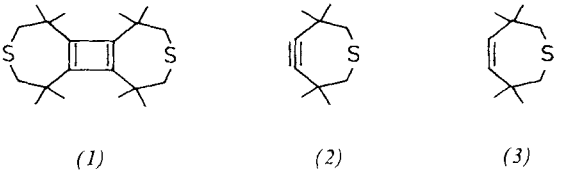
[6] *D. M. Nimrod, D. R. Fitzwater*, and *J. G. Verkade*, J. Amer. Chem. Soc. 90, 2780 (1968).

[7] *A. F. Cameron, G. Ferguson*, and *D. G. Morris*, J. Chem. Soc. *B1968*, 1249; *O. Ermer* and *J. D. Dunitz*, Chem. Commun. *1968*, 567.

Structure and Spin Multiplicity of a [4]Annulene System[1]

By *Günther Lauer, Claus Müller, Karl-Wilhelm Schulte, Armin Schweig*, and *Adolf Krebs*[*]

We have obtained the photoelectron (PE) spectrum (Fig. 1; measured at 110°C) of the cyclobutadiene derivative *(1)*[2]. The assignment of the first two bands follows from the relative intensity (①:② = 1.2:2), shape, and location [for compari-



(1) *(2)* *(3)*

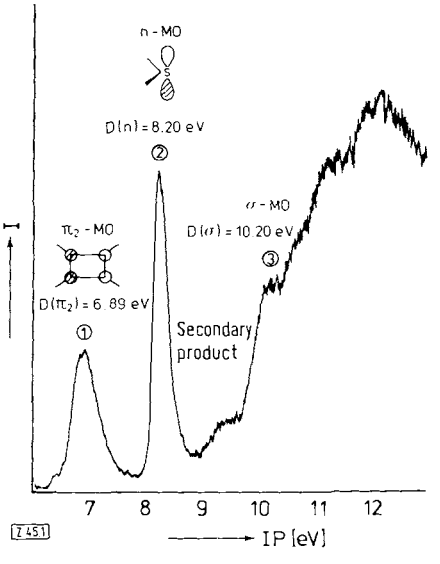


Fig. 1. Photoelectron spectrum of *(1)* with interpretation.

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son: 8.19 eV in *(2)* and 8.23 eV in *(3)*] of the band ②. Band ③ is assigned in accord with CNDO/S and MINDO/2 calculations and with the results of a semiempirical LCMO consideration (cf. 1. below) to a σ-ionization.

As a result of our findings some fundamental questions can now be answered concerning the structure (see 1. and 2. below) and spin multiplicity (see 3. and 4. below) of this [4]annulene system:

1. *Unlike the donor-acceptor-substituted cyclobutadienes*[4], *(1) possesses a cyclic-conjugated π-system.* This conclusion is reached by the LCMO method, according to which π_2 is considered as an antibonding and π_1 as a bonding linear combination of two localized olefin-π-basis MO's. The interaction of the two π-basis MO's in *(1)* follows from the measured[5] MO energies [$\pi_2 = -6.89$ eV in *(1)* and $\pi = -9.01$ in *(3)*], which give $H_{\pi\pi} = -2.12$ eV. With $0.72 H_{\pi\pi} = 2c^2\beta_{\pi\pi}$ ($c = 0.7$, where c denotes the $2p_\pi$ AO coefficient in the basis MO and the factor 0.72 takes account of the fact that only 72%[6] of the measured interaction occurs across the newly formed bonds), the resonance integral of the newly formed π-bond results as $\beta_{\pi\pi} = -1.6$ eV (for comparison: $\beta_{\pi\pi}$ of the central C—C bond in butadiene $= -2.4$ eV[7], $\beta_{\pi\pi}$ of an aromatic C—C bond $= -3.0 \pm 0.2$ eV[4]). We therefore expect the π_1 ionization at $9.01 + 2.12 = 11.1$ eV[8]. The energy-rich π_2 MO explains the good donor properties of tetraalkyl-substituted cyclobutadienes[9].

2. *Contrary to a previous hypothesis*[10], *(1) contains a* [4]*annulene system that is not influenced by the sulfur atoms.* This follows from the good agreement between the *n*-sulfur ionizations in *(1)* to *(3)* and the exclusion of transannular *n*/π interactions in *(2)*[3].

3. *(1) exists in the singlet molecular ground state.* This result follows from comparison of the measured ion energies of *(1)* (cf. Fig. 1) with the calculated[11] ion energies on ionization of the cyclobutadiene singlet(S) ground state S_0 on the one hand and of the cyclobutadiene triplet(T) ground state T_0 on the other (Fig. 2).

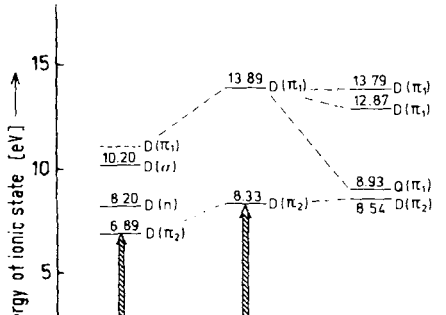


Fig. 2. Ion energies measured for *(1)* and calculated for rectangular (1.495 Å/1.319 Å [12]) singlet(S) and square (1.425 Å [12]) triplet(T) cyclobutadiene relative to the molecular ground state energies. That the $D(\pi_2)$ energy of *(1)* is lower than that of cyclobutadiene (≈ 1.5 eV) is a result of the alkyl-substitution.

For T-cyclobutadiene *two* π-ionizations, corresponding to the doublet(D) and quadruplet(Q) ion states $D(\pi_2)$ and $Q(\pi_1)$, are to be expected in the region of lower ionization potential. Experimentally, only *one* π-ionization [band ①, corresponding to the doublet ion state $D(\pi_2)$] is found in this region, as is to be expected for S-cyclobutadiene. Accordingly *(1)* exists in the singlet molecular ground state. Thus for unsubstituted cyclobutadiene also, PE spectroscopy should be the most suitable method for clarification of the multiplicity problem.

4. *The Triplet state T_0 of (1) is not detectably populated alongside the singlet state S_0 at 110 °C.* This result follows from the absence of a shoulder, corresponding to the $Q(\pi_1)$ ion state, on the flank of higher ionization potentials of band ①.

According to our findings, *(1)* possesses a true alkylated rectangular [4]annulene π-system in the electronic singlet ground state.

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CAS Registry number:
(1): 40219-42-9.

[1] Part 47 of Theory and Application of Photoelectron Spectroscopy. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 46: See [3].

[2] 3,3,7,7,10,10,14,14-Octamethyl-5,12-dithiatricyclo[7.5.0.0^{2,8}]tetradeca-1(9),2(8)diene: *H. Kimmling* and *A. Krebs*, Angew. Chem. *84*, 952 (1972); Angew. Chem. internat. Edit. *11*, 932 (1972).

[3] *H. Schmidt, A. Schweig*, and *A. Krebs*, Tetrahedron Lett. *1974*, 1471.

[4] *R. Gompper, F. Holsboer, W. Schmidt*, and *G. Seybold*, J. Amer. Chem. Soc. *95*, 8479 (1973).

[5] Assuming the validity of Koopmans' theorem: *T. Koopmans*, Physica *1*, 104 (1934).

[6] The remaining 28% of the measured interaction occurs between the $2p_\pi$ AOs which are located opposite to each other across the diagonals of the cyclobutadiene ring. The calculations which are based on the CNDO/S [11] approximation yielded (for rectangular cyclobutadiene, 1.319 Å/1.495 Å, and F = SCF operator): $\langle\pi|F|\pi\rangle = -3.0$ eV, $\langle 2p_\pi|F|2p_\pi\rangle_{bond} = -2.1$ eV and $\langle 2p_\pi|F|2p_\pi\rangle_{diagonal} = -0.8$ eV. The percentages of the calculated interaction are much independent on the specific choice of the rectangular geometry.

[7] *M. Beez, G. Bieri, H. Bock*, and *E. Heilbronner*, Helv. Chim. Acta *56*, 1028 (1973).

[8] The values for $\beta_{\pi\pi}$ and the ionization potential of the π_1-ionization rest on the assumption that the bond lengths of the double bond in *(3)* remains largely unchanged in *(1)*.

[9] *G. Maier, W. Mayer, C. Haacke*, and *R. Askani*, Angew. Chem. *85*, 1057 (1973); Angew. Chem. internat. Edit. *12*, 1016 (1973).

[10] *G. Maier* and *A. Alzérreca*, Angew. Chem. *85*, 1056 (1973); Angew. Chem. internat. Edit. *12*, 1015 (1973).

[11] CNDO/S calculations: *G. Lauer, K. W. Schulte*, and *A. Schweig*, unpublished work.

[12] *M. J. S. Dewar, M. C. Kohn*, and *N. Trinajstic*, J. Amer. Chem. Soc. *93*, 3437 (1971).

A New Mononuclear Metallo Complex with an Inhomogeneous Second Sphere in Bis(iodomercurio)hydroxomercuriooxonium Perchlorate, $[O(HgI)_2HgOH]ClO_4$[**]

By *Klaus Köhler, Gerhard Thiele*, and *Dietrich Breitinger*[*]

As a part of our studies on mercurioiodonium derivatives[1, 2] we have solved the structure of the compound formulated by *Hayek*[3] as $[Hg(HgI_2)_2](ClO_4)_2$ by X-ray analysis.

This intensely yellow compound crystallizes as trapezoid platelets from solutions of HgO and HgI_2 in 20% $HClO_4$. The crystallographic data were determined using an automatic four-circle diffractometer (Hilger-Watts, Type Y 290; $Mo_{K\alpha}$ radiation, graphite monochromator)[4] [unit cell: $a = 1047.9(4)$, $b = 1302.2(1.1)$, $c = 754.5(5)$ pm; $\beta = 90.31(3)^\circ \triangleq 1.576(1)$ rad; space group $C_{2h}^5 - P2_1/n$; $Z = 4$; $d_{X\text{-ray}} = 6.31$, $d_{pyk} = 6.25$ g cm^{-3}]. The structure was determined from 1135 independent reflections using three-dimensional Fourier methods ($R = 0.062$ after empirical correction for absorption)[2]. This model indicates that the *Hayek*[3] formulation is erroneous, and, in fact,

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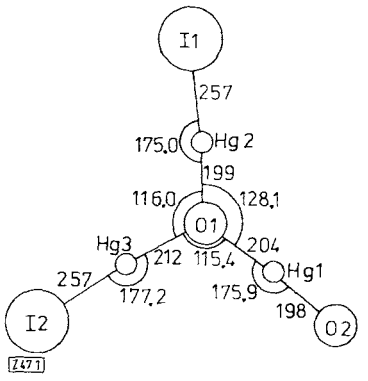


Fig. 1. Structure of the cation $[O(HgI)_2HgOH]^+$; bond lengths [pm] and bond angles [°].

planar bis(iodomercurio)hydroxomercuriooxonium ions $[O(HgI)_2HgOH]^+$ (Fig. 1) and ClO_4^- ions occur in the lattice. To our knowledge this is the first example of a mononuclear metallo complex with an inhomogeneous second sphere to be discovered.

Deviations of the heavy atom skeleton from C_{2v} symmetry are due to varyingly strong additional interactions between ClO_4^- ions and the Hg atoms of the cation; intermolecular contacts perturbing the symmetry also exist between I and Hg atoms.

The mean distance between three-coordinate oxygen and mercury $\bar{R}$(O—Hg) = 205 pm agrees with the bond lengths in $[O(HgCl)_3]^+$ (R(O—Hg) = 205 pm)[5]. The two equal bond lengths R(Hg—I) = 257 pm are significantly shorter than the corresponding values in the yellow modification of HgI_2 (R(Hg—I) = 261 pm)[6]. This effect is attributable to the formal positive charge on the central oxygen atom. Similar short bond lengths between Hg(1) and the hydroxy-oxygen O(2) (R(Hg—O) = 198(3) pm; Fig. 1) are known only for Na_2HgO_2 (R(Hg—O) = 196 pm; standard deviation not reported)[7].

The occurrence of a hydroxyl group, whose proton could not be localized by X-ray study, and which is coordinated in such an unusual way to mercury, and also the formation of weak hydrogen bonds to ClO_4^- ions, were shown by vibrational spectrometry. Vibrational spectra of the isotypic tetrafluoroborate, $[O(HgI)_2HgOH]BF_4$, prepared analogously, show that the hydrogen bonds between the complex cations and the anions are even weaker in the latter, although the spectra are otherwise in full agreement.

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CAS Registry number:
$[O(HgI)_2HgOH]ClO_4$: 52165-26-1

[1] *D. Breitinger* and *K. Köhler*, Inorg. Nucl. Chem. Lett. *8*, 957 (1972).
[2] *K. Köhler*, Dissertation, Universität Erlangen 1973.
[3] *E. Hayek*, Z. Anorg. Allg. Chem. *223*, 382 (1935).
[4] We thank Dr. *G. Liehr* for the measurements.
[5] *K. Aurivillius*, Ark. Kemi *22*, 517, 534 (1964).
[6] *G. A. Jeffrey* and *M. Vlasse*, Inorg. Chem. *6*, 396 (1967).
[7] *R. Hoppe* and *H. J. Röhrborn*, Z. Anorg. Allg. Chem. *329*, 110 (1964).

Improved Preparation of Monosodium Cyanamide

By *Stefan Weiss* and *Helmut Krommer*[*]

According to an almost hundred years old process, monosodium cyanamide (sodium hydrogencyanamide) *(1)* which is of interest as a starting material for syntheses can be obtained by treating cyanamide with sodium ethanolate in anhydrous ethanol[1]. In a search for an industrially useful method of preparation we have found that cyanamide reacts smoothly at room temperature with sodium hydroxide in an alcoholic suspension, yielding exclusively *(1)* if the reaction medium is an aliphatic alcohol containing three to five C atoms[2]. It is particulary significant that this method affords *pure* monosodium cyanamide in *quantitative yield.*

$$H_2N\text{-}CN + NaOH \xrightarrow{C_3\text{- to }C_5\text{- alkanol}} Na[HN\text{-}C{\equiv}N] + H_2O$$
(1)

Experimental:

Finely powdered sodium hydroxide (80.0 g, 2.00 mol) is added with vigorous stirring to a solution of cyanamide (84.1 g, 2.00 mol) in 2-propanol (500 ml) while the temperature is kept at 25 °C by cooling. After *ca.* 3 h a colorless, loose powder, sensitive to moisture, can be isolated by filtration and drying in a vacuum (40—50 °C): 127 g (99 %) of pure *(1)*, characterized by elemental analysis and argentometric cyanamide determination.

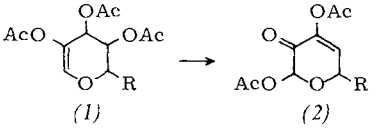
Received: April 16, 1974 [Z 49 IE]
German version: Angew. Chem. 86, 590 (1974)

[1] *E. Drechsel*, J. Prakt. Chem. (2) *11*, 311 (1875).
[2] German Pat. Appl. P 2358903.9, November 27, 1973.

Efficient Synthesis of Sugar 3,2-Enolones[1] from 2-Hydroxyglycals and Their Conversion into 4-Pyrones

By *Eleonore Fischer* and *Frieder W. Lichtenthaler*[*]

Although previously[2] formulated as hypothetical intermediates in the long known conversion of acylated 2-alduloses into kojic acid derivatives[3], sugar 3,2-enolones[1] of type *(2)* have hitherto been obtained only from hexoses in the form of 1-*O*-methyl derivatives[4], and then always by oxidation of difficultly accessible, partially acylated hexosides with subsequent β-elimination. We now describe an efficient synthesis of 1-acylated 3,2-enolones from 2-hydroxyglycal esters *(1)* → *(2)*, which is applicable to hexoses, deoxyhexoses, and pentoses and *via* the 1-halo compounds, also provides ready access to the 1-alkoxy derivatives.



(1) *(2)*

The chlorides *(4)*[6] which are the primary addition products of chlorine[5] to the perbenzoyl-2-hydroxyglycals *(3a)—(3c)* are stable only at low temperature and are extremely sensitive to hydrolysis. In the presence of water the tetrabenzoyl-2-aldosulose *(6a)* or the tribenzoyl derivatives *(6b)* and *(6c)* are obtained, a finding which is readily interpreted by formation of the partially esterified orthoacid derivatives *(5)* and their decomposition. If, however, a benzene solution of *(4)* is heated for a short time in the presence of an acid-acceptor (*e.g.* aqueous $NaHCO_3$), hydrolysis to *(6)* is accompanied by elimination of benzoic acid with formation of the 3,2-enolones *(7a)—(7c)* in yields of 50—60 % [based on *(3a)—(3c)*] (see Table 1).

Subsequent reactions of these benzoyl enolones were investigated mainly for the hexose derivative *(7a)*. With HCl/acetyl

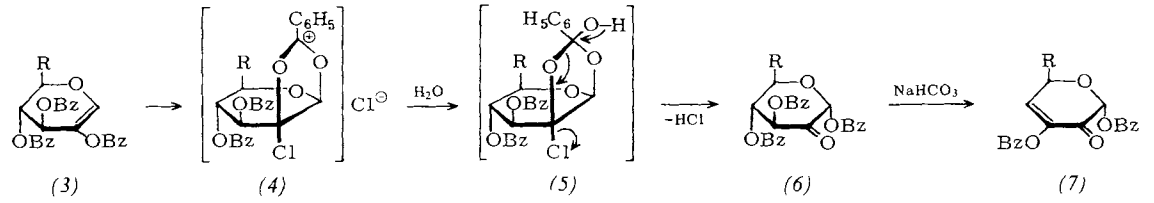
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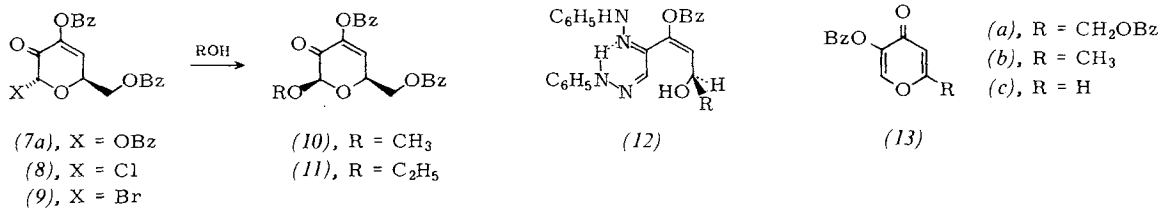
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Table 1. Physical properties of the synthesized compounds *(6)*–*(11)*.

Product [a]	Educt	Yield [%]	M.p. [°C]	$[\alpha]_D^{20}$ [b]	1-H (s)	4-H ($J_{4,5}$ [Hz])
(6a)	*(3a)*	49	60–63	+ 34	3.48	3.95 (t, 9)
(6b)	*(3b)*	34	syrup	– 0.5	3.77	4.52 (t, 9)
(7a)	*(3a)*	69	129—130	+ 6	3.31	2.92 (d, 2)
(7b)	*(3b)*	51	amorphous	+ 13	3.47	3.17 (d, 2)
(7c)	*(3c)*	65	94–95	– 40	3.45	3.02 (q, 2, 4)
(8)	*(7a)*	51	131	+ 58	3.79	3.07 (d, 2)
(9)	*(7a)*	78	151–152	+ 104	3.36	3.03 (d, 2)
(10)	*(9)*	65	111–112	– 116	5.02	3.12 (d, 4)
(11)	*(9)*	67	106	– 98	4.89	3.09 (d, 4)
(6a)-DNP	*(6a)*	46	167–169	+ 139	2.7 [c]	4.60 (t, 9)
(7a)-DNP	*(7a)*	72	149–150	+ 452	2.7 [c]	3.55 (d, 2)
(10)-DNP	*(10)*	68	209–211	– 134	4.36	3.65 (d, 4)

[a] DNP denotes the 2,4-dinitrophenylhydrazone of the corresponding compounds.
[b] In $CHCl_3$.
[c] Coincident with the aromatic protons.





chloride or HBr/glacial acetic acid, *(7a)* underwent smooth exchange of the 1-benzoyloxy group and formation of the α-halo derivatives *(8)* and *(9)* respectively, from which the β-alkyl glycosides *(10)* and *(11)* are accessible in good yield by short heating in an alcohol (see Table 1). At room temperature the enolones *(7a)* and *(10)* and the aldosulose *(6a)* smoothly give 2,4-dinitrophenylhydrazones. However, on heating with, *e.g.*, phenylhydrazine in acetic acid solution for a short time, hydrolysis of the 1-substituent occurs. As a result the aldehyde group participates in the reaction with formation of the same phenylosazone of m.p. 190 °C that is also obtained analogously from the enolones *(8)*, *(9)*, and *(11)* and is assigned structure *(12)* on the basis of these and spectroscopic data. In contrast to *(12a)*, whose rotation ($[\alpha]_D^{20} = -45°$ in pyridine) indicates considerable resistance to racemization of the one remaining center of chirality, the phenylosazone *(12c)*, m.p. 161—163 °C, prepared analogously from the pentose enolone *(7c)*, is optically inactive, as expected.

Not unexpectedly, in view of similar conversions[4b, 7], the enolones *(7)*—*(11)* show a marked tendency to form the 4-pyrone system, a fact which supports previous mechanistic concepts[2]. Thus, when heated for a short time with sodium acetate in glacial acetic acid, the hexose derivatives *(6a)*, *(7a)*, and *(8)*—*(11)* afford dibenzoylkojic acid *(13a)* in yields exceeding 80%, whilst equally smoothly 5-*O*-benzoylallomaltol *(13b)*[8] is obtained from *(7b)*, and the 3-*O*-benzoate of pyromeconic acid, *(13c)*, m.p. 153 °C[9], from the pentose enolone *(7c)*. In aqueous acid or alkali (*e.g.* 50% trifluoroacetic acid or 2 N NaOH) the free 4-pyrone *(13)*, H in place of Bz, is formed.

The structures and configurations of the compounds prepared were proved by NMR spectroscopic and rotatory findings as well as by combustion-analytical data. The β-configuration of *(10)* followed unambiguously from non-identity with the α-anomer which has clearly different physical data[4d] and affords a 2,4-dinitrophenylhydrazone of m.p. 233—234 °C, $[\alpha]_D^{20} = +390°$ ($c = 0.1$, $CHCl_3$). The dinitrophenylhydrazone of *(7a)* shows a correspondingly high positive rotation, whence also the α-configuration can be assigned, and the same configuration follows from the differing 4-H/5-H coupling constants which for the α-anomers always amount to 2 Hz as a result of the H_1^0 conformation, which is notably less than that (3.5 Hz) for the β-anomers *(10)* and *(11)* existing in the H_0^1 conformation. The α-configuration of the aldosuloses *(6a)* and *(6b)* is indicated both by the high positive rotation of *(6a)* and in particular by the chiroptical findings, which can be interpreted on the basis of the exciton chirality rule for enones[10]. Since, however, β-anomers are to be expected on decomposition of the intermediate orthoacid, the loss of HCl from *(5)* must be accompanied by C-1 epimerization—not unusual under in these conditions—leading to the more stable α-anomer.

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CAS Registry numbers:

(3a)	14125-75-8	*(3b)*	52080-34-9
(3c)	14125-77-0	*(6a)*	52080-35-0
(6a)-DNP	52080-36-1	*(6b)*	52080-37-2
(7a)	52080-38-3	*(7a)*-DNP	52080-39-4
(7b)	52080-40-7	*(7c)*	52080-41-8
(8)	52080-42-9	*(9)*	52080-43-0
(10)	52152-86-0	*(10)*-DNP	52080-44-1
(11)	52080-45-2	*(12a)*	52080-46-3
(12c)	52080-47-4		

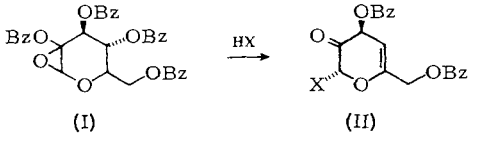
[1] Simplified designation for α,β-unsaturated glycopyranosuloses of type *(2)* in view of their derivation from the monenol form of vicinal 2,3-diketones.

[2] *H. S. Isbell*, J. Res. Nat. Bur. Standards *32*, 45 (1944); *M. G. Blair*, Advan. Carbohyd. Chem. *9*, 119 (1954).

[3] a) *K. Maurer*, Ber. Deut. Chem. Ges. *63*, 25 (1930); *K. Maurer* and *A. Müller*, *ibid.* *63*, 2069 (1930); *K. Maurer* and *W. Petsch*, *ibid.* *64*, 2011 (1931); b) *ibid.* *66*, 995 (1933); c) *K. Maurer* and *R. Böhme*, *ibid.* *69*, 1399 (1936).

[4] a) *P. J. Beynon*, *P. M. Collins*, *P. T. Doganges*, and *W. G. Overend*, J. Chem. Soc. *C 1966*, 1131; b) *F. W. Lichtenthaler* and *P. Heidel*, Angew. Chem. *81*, 998 (1969); Angew. Chem. internat. Edit. *8*, 978 (1969); c) *K. Heyns*, *P. Köll*, and *H. Paulsen*, Chem. Ber. *104*, 3096 (1971); d) *F. W. Lichtenthaler*, Methods Carbohyd. Chem. *6*, 348 (1972); e) *P. M. Collins*, *W. G. Overend*, and *B. A. Rayner*, Carbohyd. Res. *31*, 1 (1973).

[5] Addition of chlorine has been studied previously for the case of *(3a)* [3b]. A product which, from its m.p. and rotation, is clearly identical with *(7a)* was, however, assigned the structure of a 2,3,4,6-tetra-*O*-benzoyl-D-glucose 1,2-epoxide (I), and structure (II) was assigned to the 1-halo compounds *(8)* and *(9)* formed by addition of HX thereto [3c]. Hence the preparation of compounds of type (I) and (II) has not yet been accomplished.



(I) (II)

[6] *F. W. Lichtenthaler* and *E. Fischer*, Angew. Chem. *86*, 592 (1974); Angew. Chem. internat. Edit. *13*, 548 (1974).

[7] *G. J. F. Chittenden*, Carbohyd. Res. *11*, 424 (1969); *D. M. Mackie* and *A. S. Perlin*, *ibid.* *24*, 74 (1972).

[8] Needles of m.p. 128–129 °C, identical with an authentic sample prepared from kojic acid by the method of *M. G. Brown*, J. Chem. Soc. *1956*, 2558.

[9] *G. A. Garkusha*, J. Gen. Chem. USSR *16*, 2025 (1946); Chem. Abstr. *42*, 567 (1948), gives a m.p. of 152–153 °C.

[10] *M. Koreeda*, *N. Harada*, and *K. Nakanishi*, J. Amer. Chem. Soc. *95*, 266 (1974).

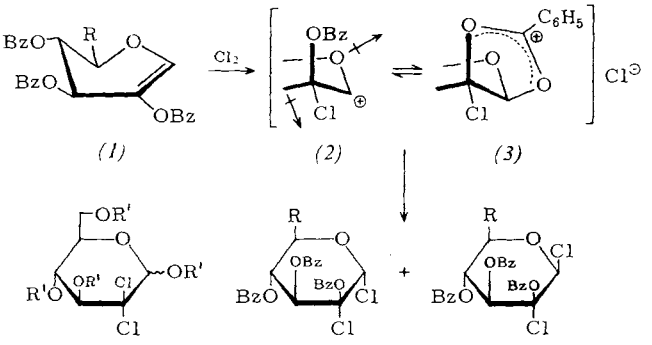
1,2-Dichlorides from 2-Hydroxyglycals: Preparation and Assignment of Configuration by the Exciton Chirality Method

By *Frieder W. Lichtenthaler* and *Eleonore Fischer*[*]

Six isomers require discussion for the chlorine-addition products of peracyl-2-hydroxyglycals *(1)*, namely the 1,2-dichlorides with the *manno/lyxo-* *(6)/(7)* or the C-2 epimeric *gluco/xylo*-configuration and the 2,2-dichloro compounds *(5)* in α- and β-form conceivably obtainable by way of 1,2-acyloxonium chloride intermediates. Hitherto it has not been possible to decide unambiguously between these possibilities although this reaction has been much investigated because the chlorine adducts can be hydrolyzed to 2-uloses[1] and some crystalline dichlorides have been characterized[2]. By synthesis of two hexose, 6-deoxyhexose and pentose dichlorides each from the perbenzoyl-2-hydroxyglycals *(1a)—(1c)*, and by the first application of the exciton chirality method[3] to determination of the configuration at a tertiary carbon atom, we have now succeeded in unequivocally assigning structures and configurations to the products and thus in elucidating the steric course of the reaction.

Chlorination of *(1a)—(1c)* in benzene or toluene (5—10 min at 25 °C) gives in each case a pair of dichlorides *(6a)—(6c)* or *(7a)—(7c)* in 1:1 to 3:1 mixtures; these products can be separated without difficulty and unambiguously characterized (cf. Table 1). They are remarkably inert, as is shown by their stability to water, silver carbonate/acetone, silver perchlorate/methanol in the cold, and towards heating with aqueous sodium hydrogen carbonate in benzene.

Compounds containing geminal chlorine substituents can be unambiguously excluded because of the non-identity of *(6a)*



(1) *(2)* *(3)*

(4), R' = H *(6)* *(7)*

(5), R' = Bz

(a), R = CH_2OBz; *(b)*, R = CH_3; *(c)*, R = H

and *(7a)* with the α- and β-tetrabenzoates obtained by benzoylation of 2,2-dichloro-D-arabinohexose *(4)*[4] (cf. Table 1), as well as by mass-spectrometric findings. Since one of the principal modes of fragmentation begins with excision of the C-1 substituent, *(6a)—(6c)* and *(7a)—(7c)* always show (M − 35) mass lines with the isotopic ratio 3:1 (loss of chloride), while the two anomers *(5)* always show a (M − 121) mass line with the isotopic ratio 3:2 owing to loss of the 1-benzoyloxy group.

That the products thus formulated as 1,2-dichlorides are in each case pairs of anomers, *i.e.* have the same stereochemistry at C-2, can be most clearly demonstrated by the reactions occurring on short heating with $TiCl_4$ in chloroform. In the

Table 1. Physical properties of the synthesized compounds *(5)—(7)*.

Product [a]	Educt	Yield (%)	M.p. [°C]	$[\alpha]_D^{25}$ [b]	CD Δε (nm) [c]	
(6a)	*(1a)*	17	158—159 [d]	+ 6	+10.2 (222)	−30.7 (239)
(6b)	*(1b)*	31	amorphous	− 94	+10.3 (221)	−48.1 (235)
(6c)	*(1c)*	23	amorphous	− 92	+11.7 (219)	−52.4 (235)
(7a)	*(1a)*	49	66—68	+ 22	+ 7.4 (220)	−11.5 (233)
(7b)	*(1b)*	4	syrup	− 16	+ 5.6 (221)	−17.5 (233)
(7c)	*(1c)*	16	177—178	−109	+ 3.5 (217)	− 4.8 (235)
(α-5)	*(4)*	25	176—177	+ 38	+ 8.9 (221)	− 9.1 (238)
(β-5)	*(4)*	23	209—210	− 17	+ 6.8 (220)	−10.2 (235)

[a] Separation by fractional crystallization from methanol [*(α-5)*, *(β-5)*, *(6a)*, and *(7a)*]; in other cases by layer chromatography on silica gel with cyclohexane/ethyl acetate (3:1).
[b] $c = 1$, in $CHCl_3$.
[c] In isooctane.
[d] The "dichlorotetrabenzoyloxyglycal" [2b] of unknown configuration (m.p. 156 °C, $[\alpha]_D^{20} = +10.3°$ in $CHCl_3$) may, in view of its rotation, be *(6a)* containing *(7a)* as impurity.

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case of the 1,2-dichlorohexoses only one of the two isomers is converted into the other, and then quantitatively—specifically *(7a)*→*(6a)* and *(7b)*→*(6b)*. This behavior can be interpreted only as a β→α anomerization[5], the initial compound having the β-configuration, while the α-configuration is to be assigned to the non-anomerizable isomer.

In accord with the above are the distinct differences in position of the 1-H signals: α-anomers *(6a)* and *(6b)* (1-H equatorial): $\tau < 2.6$; β-anomers *(7a)* and *(7b)* (1-H axial): $\tau = 3.02$ or 3.05, respectively. For the two 1,2-dichloropentoses—each isomer affords a 1:1 mixture *(6c)*⇌*(7c)* when heated with $TiCl_4$ in chloroform—the configuration at C-1 is assigned mainly on the basis of NMR data. As can be derived unambiguously from the splitting mode of the ring-CH, *(6c)* exists in the C1 conformation. From the significant correspondence of the position of the 1-H signal with those of *(6a)* and *(6b)* ($\tau < 2.6$ in each case) their equatorial orientation can be assumed and thus the α-configuration. For *(7c)*, however, long range coupling constants $J_{1,3} = 1.5$ and $J_{3,5e} = 1.0$ Hz are observed and indicate W orientation, proving the 1C conformation [cf. formula *(7c)*, Fig. 1]. This indirectly establishes the β-configuration, because only in β-anomers are the steric and energetic conditions present that permit the dipole-dipole interactions—unfavorable on the C1 form—between equatorial C-1 substituents and ring-oxygen to be compensated by transformation into the 1C conformation.

A decision between the *manno/lyxo*- and *gluco/xylo*-configuration for the anomeric pairs can be made on the basis of the chiroptical properties[6]. In its CD spectrum 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide *(8)* shows, as expected[3], two Cotton effects with opposite signs, the first of which ($\Delta\varepsilon_{234} = +44.6$) accords with the positive chirality of the benzoate chromophores on C-2, C-3, and C-4 (Fig. 1, A). On the contrary, the α-anomers *(6a)*—*(6c)* afford CD curves that are mirror images of that for *(8)* (Fig. 1 and Table 1), whence it can be concluded that they have the all-negative chiral arrangement of the benzoyloxy groups (Fig. 1C), *i.e.* *(6a)* and *(6b)* D-*manno*, and *(6c)* D-*lyxo*[7]. Due to their ready anomerization, *(7a)*—*(7c)* are to be regarded as β-anomers (cf. above), which is confirmed by the CD data—negative sign of the first Cotton effect that specifies the chirality. The effect, however, is much weaker than for the α-anomers, for example, by a factor of 3 for the hexoses, indicating considerable distortion of the C1 chair conformation towards the B1 boat form[8]. For the pentose derivatives *(6c)* and *(7c)*, however, the intensities of the first Cotton effects differ by a power of ten, this being in agreement with the fact that the total chirality derivable from the 1C conformation of *(7c)* is only very small since the rotational contributions from the interacting chromophores largely compensate each other (Fig. 1, B).

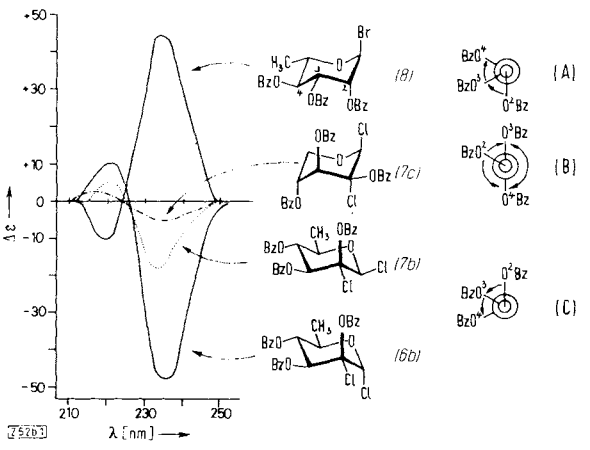


Fig. 1. CD spectra in isooctane of tri-*O*-benzoyl derivatives of α-L-rhamnopyranosyl bromide *(8)*, 2-chloro-β-D-lyxopyranosyl chloride *(7c)*, and of the anomers of 2-chloro-D-rhamnopyranosyl chloride *(6b)* and *(7b)*. The chirality directions of the benzoate chromophores on C-2 to C-4 are shown schematically by the modified Newman projections, (A), (B), and (C).

The stereospecificity of the addition of chlorine at C-2 of the 2-hydroxyglycal ester *(1)* is surprisingly exclusive; it is clearly the result of the anomeric effect on the carbon atom next to the anomeric center. It is doubtless the (in apolar solvents) unfavorable dipole-dipole interactions between the two C—O bonds of the ring-oxygen and a chlorine atom attacking from above that permits only the alternative attack by the electrophile *(1)*→*(2)* in which the electrostatic interations are reduced to a minimum [cf. dipole directions in *(2)*]. Then the dichlorides are formed from the ion pair *(2)*⇌*(3)* by combination with the gegenion; in the presence of water, however, perbenzoyl-2-aldosuloses are formed by hydrolysis[1b].

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CAS Registry numbers:

(1a) : 14125-75-8	*(1b)* : 52080-34-9	*(1c)* : 14125-77-0
(4) : 40879-11-6	α-*(5)*: 52080-48-5	β-*(5)*: 52080-49-6
(6a) : 52080-50-9	*(6b)* : 52147-64-5	*(6c)* : 52080-51-0
(7a) : 52080-52-1	*(7b)* : 52080-53-2	*(7c)* : 52080-54-3

[1] a) *M. G. Blair*, Advan. Carbohyd. Chem. 9, 107 (1954); b) *E. Fischer* and *F. W. Lichtenthaler*, Angew. Chem. 86, 590 (1974); Angew. Chem. internat. Edit. 13, 546 (1974).

[2] a) *K. Maurer*, Ber. Deut. Chem. Ges. 63, 25 (1930); *K. Maurer* and *W. Plötner*, ibid. 64, 281 (1931); b) *K. Maurer* and *W. Petsch*, ibid. 66, 995 (1933); c) *R. T. Major* and *E. W. Cook*, J. Amer. Chem. Soc. 58, 2333 (1936).

[3] *N. Harada* and *K. Nakanishi*, Accounts Chem. Res. 5, 257 (1972).

[4] *J. Adamson* and *A. B. Foster*, Carbohyd. Res. 10, 517 (1969).

[5] Cf. *K. Igarashi*, *R. Honma*, and *T. Imagawa*, J. Org. Chem. 35, 610 (1970).

[6] We are grateful to Prof. *K. Nakanishi*, Columbia University, New York, for valuable stimulation in interpretation of the CD data.

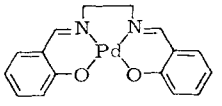
[7] For the C-2 epimers with *gluco*- or *xylo*-configuration at most a small Cotton effect is to be expected, and then probably [3] only one split into a doublet, for the chiralities between the 2,3- and the 3,4-benzoyloxy groups cancel and interaction between the 2,4-benzoyloxy groups does not contribute.

[8] The intensity is always 30% less for the anomer pair *(6a)*/*(7a)* than for *(6b)*/*(7b)*: this may be ascribed to the positive chirality contribution of the 6-benzoyloxy group which is preferably oriented *gauche* to the C-4 substituents and to the ring oxygen atom.

A Palladium(II) Complex as Hydrogenase Model

By *G. Henrici-Olivé* and *S. Olivé*[*]

A variety of microorganisms activate molecular hydrogen. This ability is ascribed to enzymes named hydrogenases which, in most cases, contain a transition metal center (iron)[1]. We wish to report on a synthetic catalyst, [2,2'-ethylenebis(nitrilomethylidine)diphenolato]palladium(II) (Pd-Salen) which, in several respects, behaves in the same way as a hydrogenase, and which therefore is considered as a suitable model.



Pd-Salen

The catalyst is prepared by reacting $Pd(NO_3)_2 \cdot 2H_2O$ with 2,2'-ethylenebis(nitrilomethylidine)diphenol (Salen) in meth-

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anol. The complex precipitates; after washing with methanol it is analytically pure. It is very poorly soluble in alcohol and in most organic solvents, but fairly soluble in DMF or pyridine. Solutions in either of these two solvents as well as suspensions of the complex in ethanol activate molecular hydrogen.

The hydrogenation of 1-hexene has been studied in DMF solution. The dependence of the reaction rate r_H on the catalyst concentration, [Cat], in the range 3×10^{-3} to 13×10^{-3} mol/l; on the 1-hexene concentration, [Olefin], in the range 0.03 to 0.3 mol/l; and on the hydrogen pressure, P_{H_2}, in the range 50 to 500 torr, is given by eq. (1) to (3):

$$r_H \sim [\mathrm{Cat}]_0 \quad (1)$$

$$1/r_H = a + b/[\mathrm{Olefin}] \quad (2)$$

$$1/r_H = a' + b'/P_{H_2} \quad (3)$$

Rate laws of essentially the same type have been reported by *Kleiner* and *Burris*[2] for the hydrogenation of methyl viologen[**] with hydrogenase extracts from *Clostridium pasteurianum*.

The rate of hydrogenation with Pd-Salen goes through a maximum in slightly alkaline solution. *Tamiya* and *Miller*[3] observed a comparable pH dependence of the activity with hydrogenase.

In C_2H_5OD, Pd-Salen catalyzes the formation of HD from H_2. The same observation with hydrogenase was interpreted by a heterolytic splitting of H_2 by the enzyme (E)[1]:

$$E + H_2 \rightleftarrows EH^{\ominus} + H^{\oplus}$$

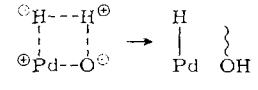
The proton is assumed to be taken up by a nonidentified "basic site" within the enzyme, where it may readily be exchanged with $D^{\oplus}$ before the backward reaction takes place. A substrate (S) is hydrogenated thus:

$$EH^{\ominus} + H^{\oplus} + S \rightarrow E + SH_2$$

We suggest an analogous mechanism for our synthetic catalyst which, however, includes a definition of the "basic site".

In Pd-Salen, the Pd center is surrounded by two nitrogen and two oxygen atoms of the planar chelating ligand, which occupy the equatorial positions. In the solid state, one of the axial positions of each surface Pd-Salen unit is occupied by the next lower unit (presumably Pd—Pd interaction). A fifth ligand appears to be necessary also in solution, since activity is observed only in coordinating basic solvents (DMF, pyridine). This leaves only one site free for coordination. The hydrogenation process, however, requires at least two vicinal sites, one for the hydrogen molecule and one for the olefin. Hence we have to assume that one or more ligands are removed from the metal in the course of the process.

The first step is presumably the coordination of a hydrogen molecule at the free site. Subsequent heterolytic splitting of the H_2 molecule probably involves a highly polarized four-center transition state; the proton is transferred to one of the oxygen anions of the chelating ligand giving a phenol group which does not occupy a coordination site at the metal.



At this stage H—D exchange between the OH group and C_2H_5OD may easily be visualized.

The new free equatorial coordination site can accommodate an olefin molecule, which is subsequently bound as an alkyl group (Alkyl-Cat-$H^{\oplus}$) by insertion into the Pd—H bond. In an intramolecular process, the proton of the phenol OH group is transferred to the alkyl giving the alkane. The original Pd-Salen complex is reformed after the alkane has left the center:

$$\mathrm{Cat} + H_2 \overset{K_1}{\rightleftarrows} H^{\ominus}\text{—Cat—}H^{\oplus}$$

$$H^{\ominus}\text{—Cat—}H^{\oplus} + \mathrm{Olefin} \overset{K_2}{\rightleftarrows} \mathrm{Alkyl—Cat—}H^{\oplus}$$

$$\mathrm{Alkyl—Cat—}H^{\oplus} \overset{k}{\rightarrow} \mathrm{Cat} + \mathrm{Alkane}$$

The rate law following from this scheme

$$r_H = \frac{k K_2 K_1 [H_2][\mathrm{Olefin}]_0[\mathrm{Cat}]_0}{1 + K_1[H_2] + K_1 K_2 [H_2][\mathrm{Olefin}]_0}$$

is in perfect agreement with the results of the kinetic measurements [eq. (1) to (3)]. The suggested mechanism is further corroborated by the finding that hydrogenation and H—D exchange occur at comparable rates (of the order of 10^{-3} mol of substrate l^{-1} s^{-1} based on 1 mol of Pd-Salen, at $P_{H_2} = 720$ torr).

The diacetyldioxime complexes of Pd and of Ni show the same behavior as Pd-Salen. Since square-planar chelating ligands are relatively frequent in Nature, we suggest that enzymes containing transition metal ions, such as certain hydrogenases, nitrogenases, *etc.* may well function according to a similar mechanism, where the "basic site" is just one anion of a chelating ligand, *e.g.* $S^{\ominus}$, $O^{\ominus}$, $COO^{\ominus}$, or $N^{\ominus}$. The catalytic process would then be characterized by a sequence of availability and non-availability of coordination sites.

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German version: Angew. Chem. 86, 561 (1974)

[1] See, *e.g.*, *B. R. James*: Homogeneous Hydrogenation. Wiley-Interscience, New York 1973.

[2] *D. Kleiner* and *R. H. Burris*, Biochim. Biophys. Acta *212*, 417 (1970).

[3] *N. Tamiya* and *S. L. Miller*, J. Biol. Chem. *238*, 2194 (1963).

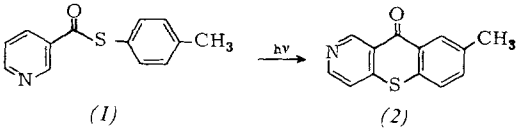
[**] Methyl viologen: 1,1'-dimethyl-4,4'-bipyridinium dichloride

2- and 4-Azathioxanthones by Photorearrangement of *S*-Aryl Thionicotinates[1][**]

By *Gerd Buchholz*, *Jürgen Martens*, and *Klaus Praefcke*[*]

S-Aryl esters of aromatic thiocarboxylic acids containing —I substituents (*e.g.* $CH_3—SO_2—$[2] or $CH_3—SO—$[3]) in the *ortho* position afford thioxanthones on "nucleophilic" photorearrangement[2,3]. No thioxanthone is formed in absence of the acceptor substituent[4].

We have now found that the positive charge on the *o*-C atom required for the photorearrangement can also be induced



(1) *(2)*

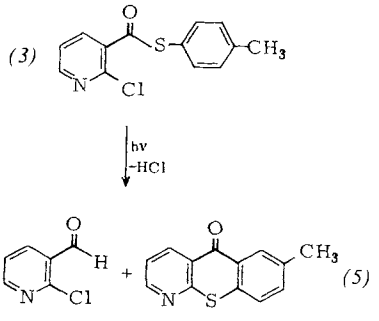
by an N atom in the ring. Irradiation[5] of *S*-*p*-tolyl thionicotinate *(1)*[6] affords a mixture of products, from which 25% of di-*p*-tolyl disulfide, 17% of *(1)* and 44% of 7-methyl-2-aza-

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thioxanthone *(2)*[7] can be isolated successively on column chromatography (residue: indefinite polymer).

On irradiation[5] of *(3)*[8,9] there are formed the hitherto unknown 2-chloro-3-pyridinecarbaldehyde *(4)*[9,10] (51%), 7-methyl-4-azathioxanthone *(5)*[11] (27%) which is isomeric with *(2)*, and di-*p*-tolyl disulfide (21%); in addition 22% of *(3)* can be isolated.



The two pharmaceutically interesting azathioxanthone systems were thus obtained for the first time by a photochemical route. It is surprising that in each case only one of the two possible isomers is formed.

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German version: Angew. Chem. *86*, 562 (1974)

[1] Organic Sulfur Compounds, Part 12. – Part 11: *G. Höhne, F. Marschner, K. Praefcke*, and *P. Weyerstahl*, Chem. Ber. *107* (1974), in press.

[2] *J. Martens* and *K. Praefcke*, Tetrahedron *30* (1974), in press, and later results.

[3] *J. Martens* and *K. Praefcke*, unpublished results.

[4] *J. Martens* and *K. Praefcke*, Chem. Ber. *107* (1974), in press.

[5] *Ca.* 70 h in anhydrous benzene after purging by very pure nitrogen, stationary N_2 atmosphere, Philips high-pressure mercury lamp HPK 125 W (quartz glass) at 20°C, 0.01 mol/l. After evaporation in a vacuum the residue is chromatographed on silica gel; elution by light petroleum (b.p. 30–70°C) with increasing concentrations of benzene.

[6] *H. Zinner* and *H. Fiedler*, Arch. Pharm. (Weinheim) *291*, 63, 330 (1958).

[7] M.p. 172–173 C; IR (CCl_4): $\nu_{C=O}$ = 1650 cm^{-1}. Cf. DOS 2044926 (1972), Takeda Chem. Ind.; Chem. Abstr. *75*, P 35989e (1971): m.p. 175 to 177°C.

[8] Prepared from the acid chloride and thio-*p*-cresol: yield 81%; m.p. 99–101 C (diethyl ether); IR (CCl_4): $\nu_{C=O}$ = 1700 cm^{-1}.

[9] Correct elemental analytical and spectroscopic data are available for all the new compounds.

[10] M.p. 42–44 C; IR (CCl_4): $\nu_{C=O}$ = 1705 cm^{-1}.

[11] M.p. 149–150 C; IR (CCl_4): $\nu_{C=O}$ = 1645 cm^{-1}. Cf. Belg. Pat. 638971 (1964), Sandoz Ltd.; Chem. Abstr. *62*, 9138a (1965): m.p. 153–154 C.

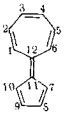
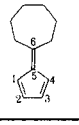
^{13}C-NMR Spectra of Heptafulvene, Pentafulvene and Sesquifulvalene[1,2][**]

By *Roger Hollenstein, André Mooser, Markus Neuenschwander*, and *Wolfgang von Philipsborn*[*]

For years much interest has been attached to the cyclic, cross-conjugated π-electron systems of heptafulvene *(1)*, pentafulvene *(2)* and sesquifulvalene *(3)* because additional resonance stabilization was expected owing to the possible dipolar resonance structures with six π-electrons[3]. In this connection particular importance is attached to the spectroscopic properties of the unsubstituted compounds which could be compared directly with the numerous quantum-chemical calculations. The ^{1}H-NMR spectra of *(1)*[4,5], *(2)*[6] and *(4)*[7,4] show marked alternation of the vicinal H,H coupling constants, thus indicating largely olefinic character of the parent compounds. The situation does not differ appreciably even for 8,8-dicyanoheptafulvene[8].

In all these cases formation of aromatic structures would be connected with charge separation. Information about the extent of this can be expected from ^{13}C chemical shifts. Experience shows that these shifts are very sensitive to changes in charge density but less affected by diamagnetic ring currents. To find the contribution of possible polarization effects of the π-system to the chemical shift of the olefinic C atoms (δ_C = 112–160 ppm) we first tried to account for the substituent effects by means of additive empirical substituent increments[9,10] and structurally similar model compounds as, *e.g.*, in the case of the pair *(4)* and *(5)*. Calculations by *Savitsky* and *Namikawa*'s method[9] neglect contributions from substituents in the γ-position, but they can be applied unambiguously also to cyclic polyenes. Experimental and calculated δ_C values are collected in Table 1.

Table 1. ^{13}C shifts (±0.2 ppm, $CDCl_3$, TMS = 0) of *(1)* [a], *(2)* [b], *(3)*, *(4)* [a] and *(5)* [b]. Calculated values in parentheses.

Compound	C atom	δ_C obs.	δ_C calc.
(1) 	1, 6	138.3	(130.8)
	2, 5	126.9 [c]	(129.7)
	3, 4	130.8 [c]	(129.7)
	7	146.6	(151.8)
	8	111.9	(109.3)
(2) 	1, 4	124.9	(130.8)
	2, 3	134.3	(129.7)
	5	152.6	(151.8)
	6	123.4	(109.3)
(3)[d] 	1	136.0 [c]	
	2	143.6 [c]	
	3	133.4	(130.8)
	4	129.9	(130.8)
	5	147.8	(152.9)
	6	114.0	(109.3)
(4) 	1, 6	137.6	(130.8)
	2, 5	133.5 [c]	(129.7)
	3, 4	134.6 [c]	(129.7)
	7, 10	118.6	(130.8)
	8, 9	129.9	(129.7)
	11	138.6	(139.1)
	12	146.5	(139.1)
(5) 	1, 4	120.0	(130.8)
	2, 3	130.0	(129.7)
	5	141.7	(139.1)
	6	160.2	(140.5)

[a] At −40°C with 5–10 molar excess of triethylamine as stabilizer.
[b] At −5°C.
[c] Assignment uncertain.
[d] C^7: 119.8; C^8, C^9: 125.4 [c], 128.2 [c]; C^{10}: 120.9.

The δ_C value of the exocyclic C atom, which should be most affected by polarization effects, accords very well with the calculated value in the case of heptafulvene *(1)*. The same is true for the ring-carbon atoms C^2, C^5 and C^3, C^4. In the pentafulvenes *(2)* and *(5)*, however, C^6 is shifted by 14.1 and 19.7 ppm, respectively, to higher frequencies. This effect was found with a large number of 6-alkyl-substituted pentafulvenes and interpreted as resulting from a *ca.* 10% contribution of polar structures to the electronic ground

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[**] This work was supported by the Schweizerischer Nationalfonds. The cooperation of Prof. *M. Rabinovitz* is gratefully acknowledged.

state[6]. The shifts of -5.9 ppm (C^1, C^4) and $+4.6$ ppm (C^2, C^3) for *(2)* also indicate polarization effects in the π-system. Benzofulvene *(3)*[11], however, shows better agreement for C^3, C^4 and C^6. The diene system of *(3)* and the heptafulvene *(1)* can thus be regarded as essentially normal conjugated olefins.

According to the ^{1}H-NMR data[7] and the ^{13}C-NMR data of the five-membered ring, sesquifulvalene *(4)* whose dipolar resonance structure contains an aromatic five-membered and seven-membered ring does not show a more extensive charge separation than is found in *(5)*. The value for C^{12} differs from the calculated value by only $+7.4$ ppm, which may indicate that the excess of positive charge found at the corresponding position in the pentafulvenes is delocalized over several C atoms in the seven-membered ring of *(4)*. In fact the sum of the shifts of C^1, C^2 and C^3 in *(4)* is greater than in *(1)*.

From the ^{13}C-NMR data it can thus also be concluded that pentafulvene *(2)*, heptafulvene *(1)* and sesquifulvalene *(4)* should be regarded as largely olefinic structures. The small extent of charge separation in these compounds is also shown by the relatively small dipole moments[12]. Formation of an aromatic seven-membered ring in *(1)* and *(4)* requires not only charge separation but also overcoming of steric strain, and it seems that the corresponding energies are not sufficiently compensated by the gain in delocalization energy.

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CAS Registry numbers:
(1): 539-79-7 *(2)*: 497-20-1 *(3)*: 2471-84-3
(4): 1961-84-8 *(5)*: 4401-17-6.

X-Ray Structure Analysis of the α-Cyclodextrin-Krypton Inclusion Complex: A Noble Gas in an Organic Matrix[**]

By *Wolfram Saenger* and *Mathias Noltemeyer*[*]

In aqueous solution, α-cyclodextrin (cyclohexaamylose, α-CD), the smallest of the cyclic oligosaccharides obtained by degradation of starch by *Bacillus macerans*, forms inclusion complexes with substances (guest molecules) whose nature extends from hydrophobic to hydrophilic, *e.g.* paraffins, aromatic compounds, fatty acids, amines, halogens, and salts[1,2]. Hydrophobic interactions, hydrogen bridge bonds, van der Waals and dipole-dipole forces have already been discussed as bonding forces that might stabilize these inclusion compounds[2], but not all of these need be considered for all types of inclusion complexes.

X-ray structure analyses of the adducts of α-CD with water[3], iodine[4] and 1-propanol[5] have clarified the nature of the conformational changes that can be observed spectroscopically during the formation of the inclusion[7]. These show that the α-CD molecule in the crystalline water adduct[3] or in "aqueous solution" takes up a strained conformation which is relaxed on formation of an adduct with any guest molecule other than water.

The structure analysis of the krypton adduct reported below was designed to explain how an apolar guest behaves that can use only van der Waals forces and in its dimensions (4 Å) resembles the water molecule (3.8 Å). The α-CD-krypton adduct first prepared by *Cramer* and *Henglein*[6] was crystallized at 3 and at 14 atm of krypton pressure (Table 1). 3900 reflexion intensities were measured for both crystals with a diffractometer, and the structures were solved and refined to a crystallographic reliability index of 8.6% in both cases.

Table 1. Crystallographic data of the α-cyclodextrin-krypton adducts.

Pressure during prepn. [atm]	3	14
Space group	$P2_12_12_1$	$P2_12_12_1$
Cell constants [Å] *a*	14.299 (7)	14.337 (7)
b	37.489 (15)	37.402 (13)
c	9.407 (4)	9.446 (4)
Measured density (flotation method) [g/cm³]	1.47	1.51
Formula content of the asym. unit	$C_{36}H_{60}O_{30}\cdot(0.78\,H_2O\cdot0.47\,Kr)\cdot5\,H_2O$	$C_{36}H_{60}O_{30}\cdot(0.28\,H_2O\cdot0.76\,Kr)\cdot5\,H_2O$

Table 2. Occupation of the voids in the α-CD molecule in the krypton adducts studied and in the water adduct. The occupation factor m amounts to 1.0 for full occupation of an atomic position. Positions that have van der Waals separations and thus can be occupied simultaneously are marked *. W = oxygen atom of the included water.

Atom	Occupation factor *m*		
	4 atm Kr adduct	15 atm Kr adduct	Water adduct
W	*0.78	0.28	
Kr(1)	0.13	0.07	
Kr(2)	0.14	0.46	
Kr(3)	*0.21	0.13	
Kr(4)	—	0.08	
W 1			*1.0
W 2			*1.0

The crystal structures of the krypton adducts formed at 3 and at 14 atm differ hardly at all in the positions of the

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[**] This work was partly supported by the Deutsche Forschungsgemeinschaft.

[1] Fulvenes, Part 13.—Part 12: *M. Neuenschwander* and *A. Frey*, Chimia *28*, 119 (1974).

[2] ^{13}C-NMR Spectroscopy, Part 6.—Part 5: *G. Müller* and *W. von Philipsborn*, Helv. Chim. Acta *56*, 2680 (1973).

[3] Cf., *e.g.*, *K. Hafner*, Angew. Chem. 75, 1041 (1963); Angew. Chem. internat. Edit. *3*, 165 (1964).

[4] *M. Neuenschwander* and *W. K. Schenk*, Chimia *26*, 194 (1972).

[5] *H. E. Zimmerman* and *L. R. Sousa*, J. Amer. Chem. Soc. *94*, 834 (1972).

[6] *R. Hollenstein*, *W. von Philipsborn*, *R. Vögeli*, and *M. Neuenschwander*, Helv. Chim. Acta 56, 847 (1973).

[7] Analysis of the AA'BB' system of the five-membered-ring protons of sesquifulvalene *(4)* (270 MHz, C_6D_6) gives $J_{7,8}=5.2$ Hz; $J_{8,9}=2.2$ Hz; $J_{7,10}=2.2$ Hz; $J_{7,9}=1.5$ Hz.

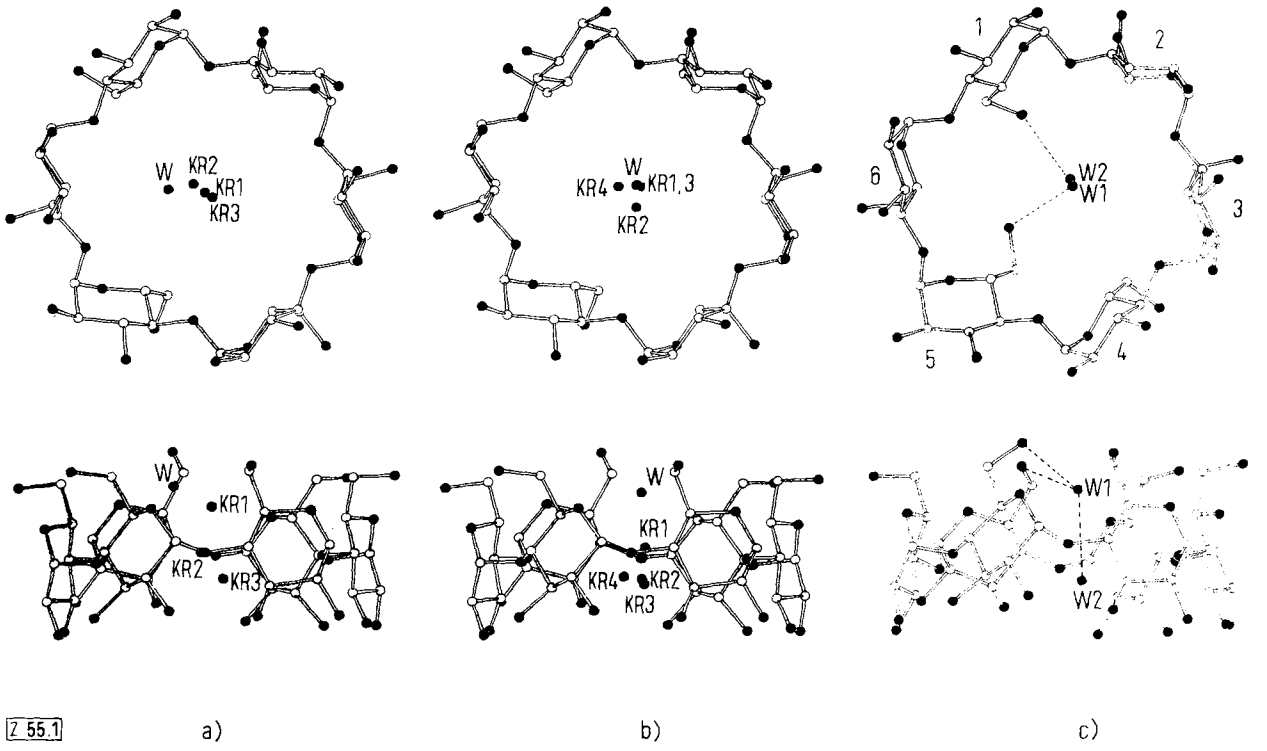
[8] *D. J. Bertelli*, *T. G. Andrews, Jr.*, and *P. O. Crews*, J. Amer. Chem. Soc. *91*, 5286 (1969).

[9] *G. B. Savitsky* and *K. Namikawa*, J. Phys. Chem. *68*, 1956 (1964).

[10] *D. E. Dorman*, *M. Jautelat*, and *J. D. Roberts*, J. Org. Chem. *36*, 2757 (1971).

[11] *M. Neuenschwander*, *H. P. Fahrni*, *H. Lehmann*, and *R. Vögeli*, Chimia *28*, 115 (1974).

[12] Pentafulvene *(2)*: 0.42 D [*P. A. Baron*, *R. D. Brown*, *F. R. Burden*, *P. I. Domaille* and *J. E. Kent*, J. Mol. Spectroscop. *43*, 401 (1972)]; for the thermally very unstable heptafulvene *(1)*: *ca.* 1.1 D; sesquifulvalene *(4)*: 2.1 D.



Z 55.1 a) b) c)

Fig. 1. Views of the α-CD-krypton adduct formed a) at 3 and b) at 14 atm; c) structure of the α-CD·2H_2O adduct. Hydrogen bonds are denoted by broken lines, the positions of the oxygen atoms of included water molecules are denoted by W and those of the krypton atoms by KR. The numbering used in the text for the six glucose residues is shown in Fig. 1c. ● = Oxygen, ○ = carbon.

α-CD and five molecules of water of crystallization, but they do differ in the krypton contents and in the positions that the noble gas atoms take up (Table 2). As Figures 1a and 1b show, the α-CD molecule exists in an almost hexagonal structure, similar to that observed in the isomorphous adducts with iodine and 1-propanol; the six C(6)—O(6) bonds point radially "outwards" from the center of the molecule. The krypton positions are only statistically occupied (Table 2). The statistical distribution of the krypton over several positions is due to its failure to fill the void in the cyclodextrin with a diameter of 4—5 Å.

For the α-CD·2H_2O adduct (Fig. 1c) the situation is substantially different: The two included water molecules are fixed in definite, fully occupied positions by hydrogen bridge bonds formed to two O(6)—H hydroxy groups that are twisted "inwards". Here, unlike the situation for the krypton adduct, the α-CD molecule fits the relatively small van der Waals radius of the water molecule (3.8 Å) because it contracts its hole by twisting the glucose residues 1 and 5. This conformation[3], which the "empty" α-CD molecule assumes also in aqueous solution before forming an inclusion compound with a molecule other than water, has an increased energy content. When a krypton atom is included, a conformational change of the α-CD molecule occurs together with a decrease in its energy content, whereby the adduct is stabilized. In addition hydrophobic interactions may stabilize the α-CD-krypton adduct, whereas van der Waals forces can hardly be of importance because of the mutually unfavorable space-filling.

Complex formation as a result of energy decrease due to conformation effects may play a general role in biochemistry, *e.g.* in enzyme-substrate interactions[8].

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German version: Angew. Chem. *86*, 594 (1974)

CAS Registry numbers:
α-Cyclodextrin-krypton adduct: 52165-27-2

[1] *F. Cramer* and *H. Hettler*, Naturwissenschaften *24*, 625 (1967).

[2] *D. W. Griffiths* and *M. L. Bender*, Advan. Catal. *23*, 209 (1973).

[3] *P. C. Manor* and *W. Saenger*, J. Amer. Chem. Soc. *90*, 3630 (1974).

[4] *R. K. McMullan*, *W. Saenger*, *J. Fayos*, and *D. Mootz*, Carbohyd. Res. *31*, 211 (1973).

[5] *W. Saenger*, *R. K. McMullan*, *J. Fayos*, and *D. Mootz*, Acta Crystallogr. (1974), in press.

[6] *F. Cramer* and *F. M. Henglein*, Chem. Ber. *90*, 2561 (1957).

[7] *D. A. Rees*, J. Chem. Soc. *B 1970*, 877.

[8] *D. E. Koshland, Jr.*, Sci. Amer. *229*, No. 10, p. 52 (1973).

Reviews

Abstracts of selected progress reports and review articles

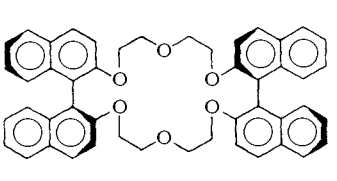
Progress in arsenic chemistry reported in 1972 is reviewed by *G. O. Doak* and *L. D. Freedman*. A brief mention of primary and secondary arsanes, including those with As—Si bonds, is followed by a detailed discussion of papers dealing with tertiary arsanes (preparation, spectra, use as ligands, chemistry, physical properties) and amino and halo arsanes. Arsonic acids have been obtained by coupling of diazotized arsanilic acid with chromanones, thiochromanones, and similar compounds, and subsequent decomposition of the coupling products with evolution of N_2. Tertiary arsane oxides can be prepared from enantiomeric tertiary arsanes without racemization by oxidation with N_2O_4. A series of publications are concerned with the reaction of tertiary arsane oxides with alkyl halides. Alkaline cleavage of arsonium salts proceeds with retention of configuration, in contrast to that of phosphonium salts. Further studies have been performed on the reactions of arsenic ylides. Additional sections are devoted to compounds with As—S bonds, cyclic As derivatives, spectroscopic studies, and analytical methods. [Arsenic. Annual Survey Covering the Year 1972. J. Organometal. Chem. *68*, 295—369 (1974); 316 references]

[Rd 706 IE—M]

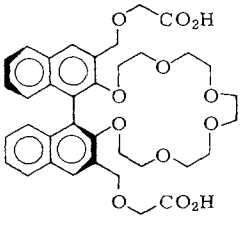
Nonbenzenoid aromatic π-electron systems is the title of a review by *F. Sondheimer*. After surveying the typical properties of benzene as the prototype of an aromatic molecule, the author examines annulenes, dehydroannulenes, bridged annulenes, ionic systems, and heteroaromatic systems to establish which properties of benzene are found in these systems and which are not. For instance, while [18]annulene, having a $(4n+2)$ π-electron system, undergoes electrophilic substitution, is almost planar, exhibits no alternation of bond lengths and a diamagnetic ring current, it is nevertheless not particularly stable, reacts rapidly with bromine, and is subject to a valence isomerization. However, its "aromatic" character becomes clear on comparison with [16]annulene. [Nonbenzenoid Aromatic π-Electron Systems. Chimia *28*, 163—172 (1974); 80 references]

[Rd 711 IE—L]

The chemistry of inclusion compounds is considered by *D. J. Cram* and *J. M. Cram*. Such complexes of organic molecules command particular interest as models for simulating the substrate selectivity of enzymes. The structure and bonding in molecular complexes of this type are discussed with reference to the crown ethers and their derivatives with the binaphthyl grouping. They can complex and lipophilize alkali metal, ammonium, and alkylammonium ions. An optically active crown ether *(1)* containing two binaphthyl groups preferentially



(SS)-(1)



(S)-(2)

complexes (>2:1) an enantiomeric form of a (1-phenylethyl)-ammonium salt. A dicarboxylic acid *(2)* having a crown ether-binaphthyl skeleton behaves similarly towards enantiomeric amino acids; this property could be utilized in an instrument for resolution of entantiomers. [Host-Guest Chemistry. Science *183*, 803—809 (1974); 22 references]

[Rd 712 IE—L]

Metabolism and function of alkaloids in plants are the topic of a survey by *T. Robinson*. Alkaloids are by no means inert final metabolic products but are degraded and synthesized in some cases at considerable rates. The degradation products and pathways are frequently unknown. Very little proof has so far been obtained for the common view that alkaloids have a protective function. [Metabolism and Function of Alkaloids in Plants. Science *184*, 430—435 (1974); 61 references]

[Rd 713 IE—L]

Base-catalyzed C—C addition reactions of hydrocarbons, in which alkali metals and organoalkali metal compounds, including potassium *tert*-butoxide in isolated cases, serve as catalysts are reviewed—with exclusion of addition reactions leading to macromolecules—in an article by *H. Pines*. The successful oligomerization of simple olefins by alkali metal in the presence of a promotor such as anthracene was first reported in 1956. In this article the author discusses the dimerization of propene, isoprene, styrene, dihydronaphthalene, the reactions of propane with butenes, and olefin ethylation with ethylene. Two or more molecules of a hydrocarbon can react with each or one another with or without hydride elimination with formation of C—C bonds. Intramolecular cyclizations of open-chain and cyclic alkenes and alkynes (*e.g.* 1,3,8,10-cyclododecatetrayne → biphenylene by potassium *tert*-butoxide in *tert*-butanol at room temperature) proceed in like fashion in the presence of strong bases. Alkylarenes containing benzylic hydrogen undergo reaction with lengthening of the alkyl group. Conjugated dienes afford alkenylarenes. Promoters are superfluous if the substrates readily yield alkali metal compounds. [Base-catalyzed Carbon-Carbon Addition Reactions of Hydrocarbons. Synthesis *1974*, 309—327; 48 references]

[Rd 714 IE—M]

Synthesis and preparative use of metal derivatives of primary and secondary arsanes, stibanes and bismuthanes are summarized in a report by *G. O. Doak* and *L. D. Freedman*. Reaction of these arsenides, stibides, and bismuthides with organohalo compounds is an important preparative method for tertiary arsanes, stibanes, and bismuthanes. These metal derivatives are also useful for the synthesis of compounds with covalent bonds between arsenic or antimony and Si, Ge, Sn, or Pb. The report deals, *inter alia*, with the cleavage of triarylarsanes, triarylstibanes, diarsanes, and bis(diarylarsenic) oxides with alkali metals. The metal derivatives are prepared by reaction of secondary arsanes and stibanes with organolithium compounds or alkali metals; primary arsanes react in a similar fashion with Na, K or organolithium reagent. Reactions of haloarsanes, -stibanes and -bismuthanes with alkali metal as well as those of alkali metal arsenides M_3As and $(M_2As)_2$ or alkali metal stibides M_3Sb and $(M_2Sb)_2$ with alkyl halides are also discussed. [Syntheses and Reactions of Arsenides, Stibides, and Bismuthides. Synthesis *1974*, 328—338; 79 references]

[Rd 715 IE—M]

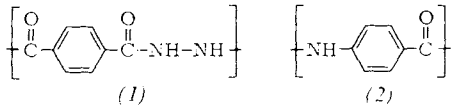
Patents

Abstracts of selected "Deutsche Offenlegungsschriften" (DOS), *i. e.* provisionally published specifications as filed with the German Patent Office

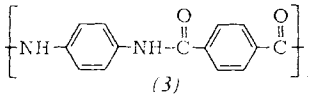
Styrene-acrylonitrile copolymers that can by processed thermoplastically and are particularly suitable for the production of CO_2-impermeable beverage bottles consists essentially of a resin that contains 76—85 wt.-% of polymerized acrylonitrile and 24—15 wt.-% of an aromatic olefin blended with a grafted rubber. The graft component contains 50—70 wt.-% of a rubber, and the grafted fraction 61—85 wt.-% of acrylonitrile and 39—15 wt.-% of aromatically substituted olefins. To enable the composition to be used for the production of impact-resistant bottles, the resin should have a melt viscosity of 2×10^4 to 4×10^5 poises at 220 °C. The polymerizations are carried out in emulsion; accurate feed recipes must be adhered to in this process. [DOS 2256612; E. I. du Pont de Nemours and Co., Wilmington, Del. (USA)]

[PR 197 IE—W]

Polyhydrazide fibers with high elasticity moduli have a content of at least 85% of the repeat units *(1)* to *(3)*. Accurate instructions are given for the composition of the polymer. Thus the maximum contents of these repeat units that may be present are 40 mole-% of *(1)*, 42.5 mole-% of *(2)*, and



(1) *(2)*

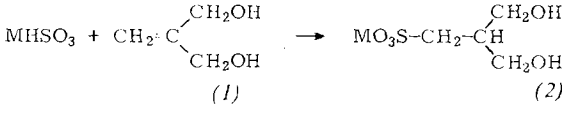


(3)

75 mole-% of *(3)*. For example, terephthalodihydrazide, and *p*-aminobenzohydrazide are dissolved with lithium chloride in hexamethylphosphoric triamide and condensed with terephthaloyl dichloride in the presence of pyridine. The solution is extruded through spinnerets into water. The resulting fibers are drawn at about 370 °C to increase their strength. [DOS 2232504; Toray Industries, Inc., Tokyo (Japan)]

[PR 198 IE—W]

Salts of 3-hydroxy-2-hydroxymethylpropanesulfonic acid *(2)* are obtained by addition of hydrogen sulfites to 2-methylene-1,3-propanediol *(1)* in the presence of oxygen, which acts as a catalyst (M = NH_4, alkali metal). The salts *(2)* are suitable

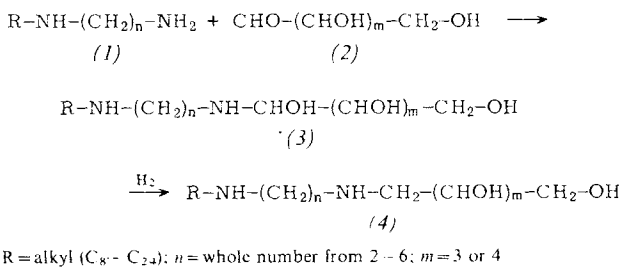


(1) *(2)*

for use as co-condensable compounds *e.g.* for the production of copolyesters for basically dyeable polyester fibers, as monomers for polyurethanes, or as intermediates for organic syntheses. [DOS 2224304; Bayer AG, Leverkusen]

[PR 199 IE—D]

***N*-Alkyl-*N'*-polyhydroxyalkylalkylenediamines** *(4)* can be used as textile-softening additives for washing products and as raw materials for the synthesis of surfactants. They can be obtained by reaction of *N*-alkylalkylenediamines *(1)*, *e.g.*



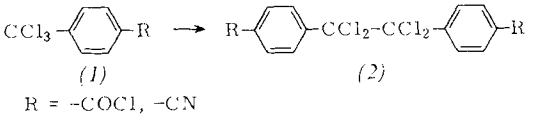
(1) *(2)* *(3)* *(4)*

R = alkyl (C_8 - C_{24}); n = whole number from 2 - 6; m = 3 or 4

N-octyltrimethylenediamine, with aldoses *(2)*, such as glucose, mannose, and arabinose, followed by catalytic hydrogenation of the reaction products *(3)*. [DOS 2226869; Henkel & Cie. GmbH, Düsseldorf]

[PR 200 IE—D]

Derivatives of 4,4'-tetrachloroethylenedibenzoic acid *(2)* are obtained by reductive coupling of the 4-trichloromethylbenzoic acid derivatives *(1)* in the presence of catalytic quantities of Cu powder or Cu ions, with the addition of chlorinatable substances such as acetone or olefins and possibly HCl acceptors to bind the chlorine released. The derivatives *(2)*, preferably the acyl chloride and the nitrile, are suitable for use



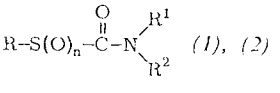
(1) *(2)*

R = -COCl, -CN

as starting materials for polymers, *e.g.* polyesters or polyamides. [DOS 2208398; Dynamit Nobel AG, Troisdorf]

[PR 203 IE—D]

Herbicidal sulfoxides and sulfones having the formulas *(1)* and *(2)* are preferably prepared by oxidation of the corresponding thiolcarbamates with 3-chloroperbenzoic acid. *(1)* and *(2)* are very suitable for use against lawn weeds. It is



(1), *(2)*

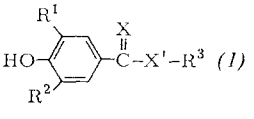
n = 1,2

(1), R = halophenyl, phenalkyl; R^1, R^2 = alkyl, cycloalkyl, benzyl, *etc.*
(2), R = alkyl, haloalkyl, alkenyl; R^1, R^2 = alkyl, cycloalkyl, alkenyl, *etc.*

well known that *S*-alkyl and *S*-benzyl *N*,*N*-dialkylthiocarbamates possess herbicidal properties. [*(1)*: DOS 2340517; *(2)*: DOS 2341119; both Stauffer Chem. Co., Westport, Conn. (USA)]

[PR 206 IE—S]

3,5-Dialkyl-4-hydroxy(thio)benzoic esters *(1)* have a morphogenetic hormonomimetic action, and are suitable for use



(1)

X, X' = O or S; R^1, R^2 = alkyl (C_3—C_6), branched; R^3 = alkyl, alkenyl, aralkyl, aryl

against insects, particularly gnats. [DOS 2339137; Chevron Research Co., San Francisco, Calif. (USA)]

[PR 207 IE—S]

The Radiation Chemistry of Macromolecules. Edited by *Malcolm Dole*. Vol. 1. Academic Press, New York—London 1972. 1st Edit., xiv, 369 pp., numerous figures, bound $ 23.—.

The effects of high-energy radiation (electromagnetic radiation, electronic radiation) on macromolecules have attracted both scientific and technical interest. The first 11 of the 14 chapters in this book deal on the one hand with the theoretical principles of radiation chemistry and on the other with the physical and chemical phenomena of the solid state.

The section on radiation chemistry is mainly concerned with the primary processes induced in matter by ionizing radiation and with the reactions of the resulting short-lived species such as ions, excited molecules, and free radicals. Special chapters are therefore devoted to the theory of free radicals and to investigations on trapped electrons in organic glasses and polymers with the aid of optical and ESR spectroscopy. The treatment of molecular mobilities and electrical conductivity in polymers is followed by a discussion of the change in the electrical conductivity in irradiated polymers. Another chapter deals with the phenomenon of thermoluminescence in polymers, which is still in its early stages as a field of research. This is followed by a chapter on the statistical theory of degradation and crosslinking, which are at present the two most important technical processes involving the application of high-energy radiation to polymers.

The last three chapters deal with experimental technique and the results of irradiation experiments on linear polyethylene as the prototype of a simple macromolecule. After the introductory theoretical chapters, this part of the volume will certainly be welcomed, since it discusses practical results of radiation chemistry and tries to correlate them with the complicated morphology of polyethylene.

The book can be recommended to anyone seeking a general picture of the processes that occur on irradiation of macromolecules. The many literature references will also help those who wish background information on the material, which is very difficult in part.

Christel Schneider [NB 206 IE]

Molecular Geometry. By *R. J. Gillespie*. Van Nostrand Reinhold Comp., London 1972. 1st Edit., ix, 228 pp., numerous figures and tables, bound *ca.* DM 38.—

In past monographs, inorganic structural chemistry has been marked by the crystal-chemical approach. It is therefore all the more commendable that the structure of isolated molecules, together with inorganic stereochemistry, is given precedence in the present book.

However, the general title forms a cover for the special approach developed earlier by the author together with *R. S. Nyholm*, the "*valence shell electron pair repulsion theory*" (VSEPRT). This theory assigns spherical spaces around the closed shell of the core electrons to pairs of free and valence electrons as proposed by *Bent*, and derives the molecular geometry from the magnitude of the electron pair repulsion. This concept is presented and extended in the first third of the book. It is remarkable that in a book with this title, neither elements of group theory nor ideas such as orbitals or hybridization are required in the development of a concept of bonding and structure, a concept that will be greatly appreciated by the practical worker; S means sulfur, and never denotes either entropy or an axis of rotation-reflection. At the same time, however, this is a danger of the book, which is undoubtedly intended to appeal mainly to students: alternative views (such as the hypervalent bonding theory) are omitted altogether, or else an attempt is made in an appendix to provide a connection with the MO approach. This becomes particularly clear in examples such as F^-, which should not exist according to p. 38, or in postulates such as that of a second valence shell invoked to explain the paramagnetism of O_2 ($\cdot\{:O\equiv O:\}\cdot$ with a triple bond; pp. 84/85).

The strength of the book lies in the second part, which presents an unusually thorough survey of the structural types of compounds, arranged according to elements of the first, then the second and higher periods of the periodic system and transition metals. Here again molecular structures take precedence over ionic lattices, and a large number of diagrams (not always of uniform quality) are included for greater clarity. The emphasis is clearly placed on non-tetrahedral and non-octahedral structures; polyhedral structures are derived in an understandable manner.

On the whole the book gives a competent subjective account of inorganic stereochemistry, and can be recommended to anyone who is familiar with the limitations of the VSEPRT and with alternative approaches.

Hans Bürger [NB 208 IE]

Metal π-Complexes, Vol. II. Complexes with Mono-Olefinic Ligands. By Max Herberhold. Elsevier Publishing Company, Amsterdam—London—New York. Part I: General Survey, 1972, 1st Edit., xv, 643 pp., 206 figs., 85 tables, bound *ca.* DM 295.—. Part 2: Specific Aspects, 1974, 1st Edit., xvi, 508 pp., 106 figs., 51 tables, bound *ca.* DM 250.—

Hardly any other field has developed so rapidly over the past 20 years as the chemistry of transition metal π-complexes. Until now there has been no general survey of existing knowledge in the field of π-complexes with monoolefinic ligands. The publication of both parts of a detailed monograph on this subject is therefore very welcome. After a historical introduction, the first part deals with general preparative methods. Two long chapters then describe the chemistry of transition metal complexes with olefins, and specifically a) with olefins having no functional groups (the material is arranged here according to the metal) and b) with olefins containing functional groups (arranged according to the functional group).

The second part considers spectroscopic studies, X-ray structures, stability of the olefin complexes, the theory of metal-olefin bonding, and the use of these compounds in industrial processes.

The first part covers the literature comprehensively up to 1968. An appendix lists 210 publications from the years 1969 and 1970; this gives some idea of the annual growth of this field. In the second part, the literature up to 1970 is included, and an appendix lists 239 further references from the period up to the middle of 1972.

The plan of the first part is broad. Physical properties and chemical reactivity are discussed in detail. Clarity is aided by numerous tables and summaries in the form of formula schemes. The overall impression reflects the author's years of experience in this field and his attention to detail.

Opinions may be divided with regard to the arrangement of the material and the classification principle. In the reviewer's opinion, a discussion of the theory of metal-olefin bonding at the beginning of the book would have helped the reader to understand many of the systematic relationships. The brief note on the historical development of bonding theories on

pages 15 to 19 would have been a good starting point for this discussion. The separate treatment of the π-complexes of pure olefins and of olefins containing functional groups makes it more difficult for the reader to trace relationships between the structure of the olefin and the properties of the complexes, particularly as a function of the metal. This arrangement also makes repetitions inevitable (compare *e.g.* pages 88 to 90 and 335 to 336). However, the excellent subject index and the author index are helpful in this respect.

For the specialist particularly this first volume is a real treasure house. It contains an abundance of interesting information that would certainly not appear in normal surveys and reviews, and that will undoubtedly stimulate new investigations. The author could possibly have taken more opportunities to direct the reader's attention to questions that are still unanswered.

Both parts have been carefully produced, and the reviewer has been unable to find any serious printing errors, a point that is particularly pleasing in connection with the references. A missing H in the structural formula of tetracarbonyl(pyrrolidine)iron (Part 1, p. 77) was also missing in the original publication. The author and the publishers are particularly to be commended for their care.

In the second part an attempt by the author to give an interpretative survey is sometimes missed too. An indication of corresponding specialist publications such as Kellers' "NMR-Untersuchungen an Komplex-Verbindungen" would help here. On the other hand there are again numerous excellent tabular summeries and reaction schemes. The completeness of the information can also be relied upon. In the chapter on IR spectroscopy, a short mention of the CO stretching vibrations of the olefin-carbonylmetal complexes would have been useful, since in practice they are often used for characterization and for the detailed study of the bonding in these complexes.

This two-part monograph will be an indispensable aid to anyone working in the field of metal-olefin complexes, regardless of whether he is seeking an introduction or has already had many years' experience. The corresponding hope, expressed in the foreword, is fulfilled in every respect. This monograph should indeed find a wide readership, even though some hearts may sink at the price.

Ernst Koerner von Gustorf [NB 209 IE]

2200 Begriffsbestimmungen nach DIN (Deutsch und Englisch) (2200 DIN Definitions (German and English)). By *H. G. Freeman.* Beuth-Vertrieb GmbH, Berlin—Cologne—Frankfurt/M. 1972. 1st Edit., 352 pp., bound DM 35.50.

This book lists in alphabetical order 2200 keywords selected from approximately 4000 DIN specifications. The keywords belong to the fields of mechanical engineering, electrical engineering, metallurgy of iron and other metals, techniques of welding, soldering, measuring, control devices, X-rays, plastics, adhesives, coatings, the testing of materials, physics, and chemistry. The keywords are explained by definitions laid down by Standards Institutes and, if necessary, by additional annotations. The corresponding English or rather British definition (adapted to British Standards) is supplemented by an explanation corresponding to the meaning of the German text. For each keyword the original DIN specification from which the word stems is listed. Homonyms are listed consecutively. In the second part the English terms are compiled in alphabetical order, without definitions but with the German terms and the field to which the terms belong. The book is supplemented by a list of standard specifications containing translations of technical terms into English and other languages. The standard specifications are classified according to the Standards Institute.

For the first time, a work compiling information scattered over many standard specifications has become available, which can be used even by those not familiar with the standards. This carefully written book will constitute a valuable tool for the specialized translator and is an indispensable addition to the many technical dictionaries already in existence.

Christian Weiske [NB 211 IE]

Interpretation of Mass Spectra of Organic Compounds. By *M. C. Hamming* and *N. G. Foster.* Academic Press, New York—London 1972. 1st Edit., xiv, 694 pp., numerous figures and tables, bound $ 37.50.

The mass spectrometer is still regarded by many organic chemists as a costly but very precise instrument for the determination of molecular weights and empirical formulas and is used accordingly. The utilization of the information contained in a mass spectrum for the determination of molecular structures often fails on account of the complexity of the problem and the lack of simple, comprehensive, and generally applicable principles of interpretation. Many attempts have been made to overcome this problem in countless textbooks and studies, generally with reasonable success; the book in question represents another independently conceived attempt.

The book is intended as an introduction to organic mass spectroscopy, but it opens up interesting possibilities for the specialist on account of its comprehensive literature index and carefully compiled bibliography.

The authors first describe in condensed form the instrumental basis of mass spectroscopy and the general properties of mass spectra, the influence of instrumental and material parameters on spectra, and the types of ions encountered. Sample manipulation and injection techniques are described in great detail. This is followed by a summary of fragmentation reactions. In contrast to many textbooks on this subject, there is not much discussion of the fragmentation pattern of different classes of substances; instead, after discussing the most important breakdown mechanisms (8 types of simple bond cleavage, 5 rearrangement reactions) and their occurrence in relation to the existence of certain structural elements, a strategy is slowly developed, which should allow a step by step integration of the mass spectrum of a substance and lead to its identification. This strategy culminates in a schematic procedure, which requires a specific rectangular arrangement of the mass spectra; the interpretation is then achieved by means of "interpretation maps" (39 interpretation maps are listed in the appendix). This is undoubtedly an interesting and stimulating attempt, but it is based largely on hypothesis, for the method is still far from perfection. Finally, computer processing of mass spectroscopic data assumes an important place in the book.

A few of the book's drawbacks cannot be overlooked. The broad epic style, in addition to lack of accuracy and clarity, does not facilitate reading. The very small number of illustrated mass spectra is remarkable. In comparison with the length of some other chapters, the treatment of metastable transitions and of pertinent modern techniques of measurement is much too short. Nevertheless, the book can be recommended to students and specialists, particularly on account of the wealth of information it contains.

Jörn Müller [NB 212 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal.

Thermodynamik. Methode zur Beschreibung stofflicher Systeme. Lehrbuch für Wissenschaftler. By *D. Schuller*. From the series "Uni-Text". Friedr. Vieweg + Sohn, Braunschweig 1973. x, 325 pp., stitched DM 36.—.

Contents: Definitionen; thermische Zustandsgleichung; kalorische Zustandsgleichung; Zweiter Hauptsatz; thermodynamisches Gleichgewicht; Nernstsches Wärmetheorem.

Lehrbuch der analytischen und präparativen anorganischen Chemie. By *G. Jander* † and *E. Blasius*. S. Hirzel Verlag, Stuttgart 1973. 10th revised Edit., xxii, 541 pp., bound DM 32.—.

Contents: Theoretische Grundlagen; Allgemeine Arbeitsgrundlagen; Analytischer Teil; Präparativer Teil · Tabellenanhang.

Advances in Biosciences, Vol. 10. Schering Workshop on Contraception: The Masculine Gender. Edited by *G. Raspé*. Pergamon Press, Oxford/Vieweg, Braunschweig 1973. VII, 331 pp., bound, DM 54,—.

Industrial Gums. Polyaccharides and Their Derivatives. Edited by *R. L. Whistler*. Academic Press, New York 1973. 2. Edit., XII, 807 pp., bound, $ 45.00.

Modern Methods of Steroid Analysis. Edited by *E. Heftmann*. Academic Press, New York 1973. xx, 523 pp., bound $ 37.50.

Contents: Chromatography; Mass Spectrometry; Infrared and Raman Spectroscopy; NMR; X-ray Diffraction; Optical Rotatory Dispersion; Circular Dichroism; Radioisotope Methods.

Practical Liquid Chromatography. By *S. G. Perry, R. Amos*, and *P. I. Brewer*. A Plenum/Rosetta Edition, Plenum Publishing Corporation, New York 1973. xiii, 230 pp., stitched $ 9.14.

Contents: Band Spreading; Adsorption Chromatography; Liquid Partition Chromatography; Exclusion Chromatography; Thin-Layer Chromatography; Column Chromatography.

Die Struktur der Atome und Moleküle. By *J. Barrett*. Verlag Chemie GmbH, Weinheim 1973. 348 pp., stitched DM 38.—.

Methoden der organischen Elementar- und Spurenanalyse. By *F. Ehrenberger* and *S. Gorbach*. Verlag Chemie GmbH, Weinheim 1973. xvi, 452 pp., bound DM 129.—.

Terpenoids and Steroids, Vol. 3. Edited by *K. H. Overton*. The Chemical Society, London 1973. x, 527 pp., bound £ 12.00.—A volume in the series "Specialist Periodical Reports".

Electrochemistry, Vol. 3. Edited by *G. J. Hills*. The Chemical Society, London 1973. ix, 250 pp., bound £ 8.00.—A volume in the series "Specialist Periodical Reports".

Transport Mechanisms in Epithelia. Edited by *H. H. Ussing* and *N. A. Thorn*. Munksgaard, Copenhagen 1973. 627 pp., bound D. Kr. 220.00.—Proceedings of the Alfred Benzon Symposium V held at the premises of the Royal Danish Academy of Sciences and Letters, Copenhagen, 10—14 September 1972.

Organic Quantum Chemistry Problems. By *R. Zahradnik* and *P. Čársky*. A Plenum/Rosetta Edition, Plenum Publishing Corporation, New York 1973. x, 222 pp., stitched $ 6.84.

IR-Theory and Practice of Infrared Spectroscopy. By *N. L. Alpert, W. E. Keiser*, and *H. A. Szymanski*. A Plenum/Rosetta Edition, Plenum Publishing Corporation, New York 1973. xiv, 380 pp., stitched $ 9.14.

Contents: Introduction; Instruments; Accessories; Theoretical Considerations; Structural Analysis; Quantitative Analysis; Sample-Handling Techniques; Spectra and Reference Library.

Chemistry and Physics of Carbon, Vol. 11. Edited by *P. L. Walker, Jr.* and *P. A. Thrower*. Marcel Dekker, New York 1973. x, 329 pp., bound $ 28.50.

Contents: Carbon Fibers; Pyrolytic Graphite; Deformation Mechanisms; Carbon Films.

Rodd's Chemistry of Carbon Compounds, Vol. III: Aromatic Compounds, Part C: Benzenoid Compounds With More Than One Nitrogen Atom in Substituent Groups. Edited by *S. Coffey*. Elsevier Scientific Publishing Company, New York 1973. xii, 334 pp., bound $ 40.00.

Organometallic Chemistry, Vol. 2. Edited by *E. W. Abel* and *F. G. A. Stone*. The Chemical Society, London 1973. xviii, 612 pp., bound £ 13.00.—A volume in the series "Specialist Periodical Report".

Organic Chemistry Series One, Vol. 9: Alkaloids. Edited by *K. Wiesner*. From the series "MTP International Review of Science". Edited by *D. H. Hey*. Butterworths/University Park Press, London 1973. 346 pp., bound £ 10.00.

Contents: Lycopodium Alkaloids; Indole Alkaloids; Tuberostemonine; Stemona alkaloids; Spirobenzylisoquinoline Alkaloids; Benzylisoquinoline and Homobenzylisoquinoline; Steroid Alkaloids; Amaryllidaceae Alkaloids; C_{19}-Diterpene Alkaloids.

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Antimetabolites of Coenzyme Q. Their Potential Application as Antimalarials

By Thomas H. Porter and Karl Folkers[*]

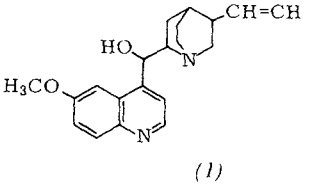
Malaria is transmitted to man by the bite of the female Anopheles mosquito, man acting as the intermediate host, and the mosquito as the definitive host for the plasmodia. Plasmodia are found to have become resistant to certain chemotherapeutic agents. A new fundamental approach to malaria chemotherapy is based on the biochemical rationale of inhibition of the electron transfer mechanism in the metabolism of plasmodia by antimetabolites of coenzyme Q, which is essential for electron transfer. Coenzyme Q refers to 2,3-dimethoxy-5-methyl-1,4-benzoquinones with isoprenoid chains of varying length on C-6. In this progress report a series of synthetic antimetabolites are presented together with a discussion of their action in current pharmacological tests.

1. Malaria—Still a Widespread Disease

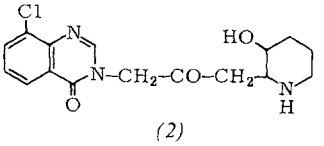
Malaria, a disease of the blood system caused by protozoa of the genus *Plasmodium*, is perhaps the most worldwide of all human diseases. According to a new treatise by *Steck*[1] at least one-tenth of the human race suffers from malarial disease each year despite all attempts both therapeutically and prophylactically to control the disease. It is still the most devastating of the infectious diseases of man. The millions of infections and many hundreds of thousands of deaths that occur each year demonstrate that malaria constitutes a global problem that has not yet been eliminated[1].

Malaria is transmitted to man by the bite of the female *Anopheles* mosquito, man acting as the intermediate host, and the mosquito as the definitive host for the plasmodia. Control of malaria has been effected by the public health measures of eradication of the mosquito vector by chemical agents and destruction of breeding areas; numerous chemotherapeutic agents have been developed for treatment of the illness.

In chemotherapy, two natural product antimalarials which have withstood the test of time and have proved effective are quinine *(1)* and febrifugin *(2)*. However, because of the threat of restricted quinine supplies during the World Wars, these drugs have gradually been replaced by synthetic chemotherapeutic agents such as chloroquine *(3)*, primaquine *(4)*, amodiaquine *(5)*, proguanil *(6)*, and pyrimethamine *(7)*.



(1)

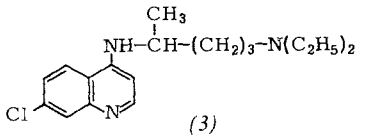


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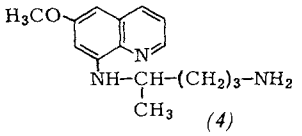
Between about 1948 and 1950 the resistance of plasmodia to certain chemotherapeutic agents became a significant problem following the discovery in Malaya of the resistance of *Plasmodium falciparum* and *Plasmodium vivax* to proguanil *(6)* (cf. Ref. [2]). Since then the resistance to other important antimalarials has been reported from many other countries of the world, including Africa and South America.

As certain strains of plasmodia have been found to be resistant to conventional antimalarial drugs, such as chloroquine *(3)* and primaquine *(4)*[3–5] new approaches to malaria chemotherapy have had to be sought by many investigators. One new and fundamental approach is based on the biochemical rationale of an inhibition of the electron transfer mechanism in the metabolism of plasmodia; this approach forms the main theme of the present progress report.

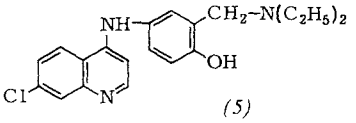
[*] Prof. Dr. K. Folkers and Dr. T. H. Porter
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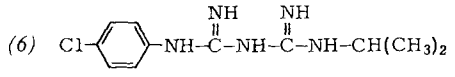
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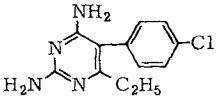
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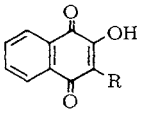
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(7)

2. Early Research on Naphthoquinones as Antimalarials

As early as 1942, as the result of a screening program in the search for new antimalarial agents, hydrolapachol *(8)* and two structurally similar quinones *(9)* and *(10)* were found to possess antimalarial activity against *P. lophurae* in ducks. These results stemmed largely from the prodigious researches carried out by *Fieser* and *Leffler* and their respective co-workers on quinones, particularly the naphthoquinones[6, 7].



(8), R = $(CH_2)_2$–$CH(CH_3)_2$
(9), R = $(CH_2)_8$–$C(n\text{-}C_5H_{11})_2$ (OH)
(10), R = $(CH_2)_3$–(cyclohexyl)

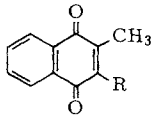
Emerging from all this effort were, *inter alia*, clinical data on two naphthoquinones *(9)* and *(10)*, which showed antimalarial activity in man[6]. In the case of *(9)*, it was stated that "two patients left the hospital in perfect condition with no parasites in the blood ... or without relapse"[6]. For *(10)*, it was said that the "effect was not satisfactory, but enough to show ... definite antimalarial activity in man"[6].

In 1943, *Bauer* found that some of these 2-alkyl-3-hydroxy-1,4-naphthoquinones were also effective prophylactic agents against malaria in chickens[8–10]. Administration of such quinones, in adequate dosage prior to and for about five days after the inoculation of chickens with sporozoites of *P. gallinaceum*, provided complete protection. In further investigations it was established that these naphthoquinones destroyed the exoerythrocytic forms of the malarial parasite which were in the reticuloendothelial cells of chicks infected with *P. gallinaceum*[9, 10].

Research on the mode of action of these quinone antimalarials was limited during the 1940's, althouth certain data did indicate interference with cell respiration. About 1945, *Wendell*[11] found that 2-alkyl-3-hydroxy-1,4-naphthoquinones were indeed potent inhibitors of respiratory systems. At concentrations of *ca.* 1×10^{-6} mol/l, 2-(3-cyclohexylpropyl)-3-hydroxy-1,4-naphthoquinone *(10)* reduced the respiration of parasitized erythrocytes by about 50% in blood drawn from a duck infected with *P. lophurae*. The results of these studies also indicated that these compounds interfere with carbohydrate metabolism and cause accumulation of lactic acid in the organism.

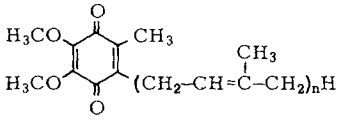
3. Discovery of Coenzyme Q_8 in Plasmodia

The structural similarity between the compounds *(8)*—*(10)* and vitamin K *(11)* formerly implied that the antimalarial activity of these naphthoquinones was the result of antagonism of vitamin K. Such a concept appeared reasonable, for it was known that vitamin K participates in the metabolism of many microorganisms, although the presence of vitamin K in plasmodia had still not been established, and apparently not even sought for.



(11a), K_1, R = Phytyl

(11b), K_2, R = $(CH_2\text{-}CH{=}C(CH_3)\text{-}CH_2)_nH$



(12), coenzyme Q

Smith et al.[12, 13] reported that 2-(3-cyclohexylpropyl)-3-hydroxy-1,4-naphthoquinone *(10)* produced a hemorrhagic syndrome and hypoprothrombinemia in young rats, and that the development of these symptoms was prevented by simultaneous administration of vitamin K. These authors' data also implied the existence of a form of vitamin K in plasmodia.

It was not until after these studies on naphthoquinone antimalarials that coenzyme Q (ubiquinone) *(12)* was discovered, and its widespread presence in living systems and its role in cell respiration, *e.g.* in succinate-dehydrogenase- and NADH-dehydrogenase-coenzyme Q[*] enzyme systems, was established (cf. Ref. [14]).

Hendlin and *Cook*[15] and *Takemari* and *King*[16] demonstrated the inhibition of succinate-dehydrogenase by certain 2-hydroxy-1,4-naphthoquinones and its reversal by coenzyme Q_{10}[**]. Similarly, *Howland*[17] demonstrated the inhibition of mitochondrial NADH-dehydrogenase by 2-alkyl-3-hydroxy-1,4-naphthoquinones.

Since 1958, it has been known that microorganisms biosynthesize and apparently use vitamin K and/or coenzyme Q in their oxidative metabolism. Consequently, one could also assume that vitamin K and/or coenzyme Q are present in plasmodia, since the occurrence of mitochondria in plasmodia, particularly in its later stages of development, had already been documented[18, 19].

It was predicted that coenzyme Q could exist in plasmodia as an intrinsic component of metabolism, and that the antimalarial activity of naphthoquinones *(8)*, *(9)*, and *(10)* could, at least in part, be due to inhibition of coenzyme Q in the manner of antimetabolites.

[*] These enzymes are also known as "succinoxidase" and "DPNH-oxidase", respectively.

[**] The subscript denotes the number *n* of isoprene units.

The search for the presence of coenzyme Q in plasmodia was successful; in 1967 *Rietz*, *Skelton*, and *Folkers* reported the occurrence of coenzyme Q_8 and Q_9 in *P. lophurae*[20, 21]. Mass spectral data and reversed-phase paper chromatographic results showed that CoQ_8 and possibly CoQ_9 were present in parasitized duck blood and could be biosynthesized by *P. lophurae*. Vitamin K was not detected in lipid fractions by reversed-phase paper chromatography.

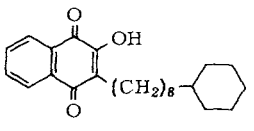
Skelton, *Lunan*, and *Folkers*, in collaboration with *Schnell*, *Siddiqui*, and *Geiman*[22], next demonstrated that the [^{14}C]-coenzymes Q_8, Q_9, and perhaps Q_7 are biosynthesized from [^{14}C]-*p*-hydroxybenzoic acid in parasitized blood; the authors isolated these coenzymes from the blood cells of rhesus monkeys which were parasitized with *P. knowlesi*. It was then shown by *Skelton et al.*[23] that CoQ_8 was biosynthesized in the blood of rhesus monkeys infected with *P. cynomolgi* and in the blood of mice infected with *P. berghei*. Again, the presence of vitamin K in plasmodia could not be detected, neither by reversed-phase paper chromatography nor by mass spectral analysis, nor by a labeling method using *in vitro* cultures of *P. knowlesi* that had been incubated with [^{14}C]-shikimic acid, a precursor in the biosynthesis of vitamin K.

Schnell et al.[24] also demonstrated the biosynthesis of coenzymes Q_8, Q_9, and Q_{10} in *Aotus* blood cultures infected with *P. falciparum*; but only the CoQ_{10} was intrinsic to the mammalian cells.

With the establishment of the presence and biosynthesis of coenzyme Q_8 as the dominant coenzyme Q (compare Ref. [25]) in plasmodia and the apparent absence of vitamin K, it seemed reasonable that such naphthoquinones as *(8)*, *(9)*, and *(10)* could actually exert at least part of their antimalarial activity by interference with the biosynthesis and/or the function of CoQ_8 in the metabolism of plasmodia. Also, it was now clearly evident that the synthesis of new analogs of coenzyme Q, rather than of vitamin K, opened up a biochemically valid and previously unexplored approach to new and effective antimalarials and to other chemotherapeuticals.

4. Synthesis and Antimalarial Activity of Menoctone

In 1967, *Fieser* and *Archer* and their respective associates[26] synthesized additional members of the 2-(ω-cyclohexylalkyl)-3-hydroxy-1,4-naphthoquinone series, including the new naphthoquinone derivative menoctone, 2-(8-cyclohexyloctyl)-3-hydroxy-1,4-naphthoquinone *(13)*, which has since been extensively investigated as an antimalarial agent both curatively and prophylactically.



(13)

In mice infected with *P. berghei*, menoctone showed activity (T − C = 6.2)[*] at 20 mg/kg and 4/5 cures at 160 mg/kg in the routine one-dose (sc) treatment[23]. However, at a dose level of 640 mg/kg, menoctone exhibited toxic effects; this dosage led to only 2/5 cures and 3/5 deaths[27].

[*] (T − C) is defined as the change in survival time (in days) of treated and untreated (control) animals.

For comparison: chloroquine *(3)*, when it was given orally at a dose of 5 mg/kg once a day for five days to groups of five mice, consistently cleared the blood of parasites in all mice for the entire test period of 28 days[28]. Similar results were obtained with menoctone, but at a daily dose rate of 25 mg/kg for five days[28].

Menoctone was also highly effective prophylactically. In 1968 *Berberian et al.*[29] reported that menoctone afforded mice more protection than primaquine *(4)* when the drugs were administered orally twice daily throughout the course of the preerythrocytic cycle. Two and a half times as much primaquine had to be given to the mice to afford complete protection [(number of parasite-free animals/number of surviving animals on the *n*th day after infection) = 1]. Moreover, oral toxicity data showed that menoctone *(13)* was 1/15 as toxic as primaquine *(4)*.

5. Inhibition of Coenzyme Q Enzymes by Chloroquine *(3)* and Menoctone *(13)*

After having established the presence of CoQ_8 in plasmodia it seemed appropriate to test already known antimalarial drugs and also the extensively studied naphthoquinone, menoctone *(13)*, *in vitro* to see if they actually do have antimetabolite activity for coenzyme Q. Subsequently, both chloroquine *(3)* and menoctone *(13)* were found by *Skelton et al.*[30] to inhibit the NADH-dehydrogenase coenzyme Q system. Chloroquine diphosphate depressed NADH-dehydrogenase activity to 70, 60, 50, and 17% when levels of 25, 50, 100, and 1000 nmoles, respectively, were added to the intact system supplemented with 100 nmoles of exogenous CoQ_{10}. Menoctone proved to be a far much more potent inhibitor in this *in vitro* system; as found by *Szarkowska*[31], at levels of 1, 10, and 25 nmoles in an intact NADH-dehydrogenase system in the presence of 100 nmoles CoQ_{10}, it depressed enzyme activity to 83, 12, and 11%, respectively, of the CoQ_{10}-treated control system[30].

Current research by *Crane et al.*[32] on mitochondrial electron transport indicates that chloroquine *(3)* inhibits oxidation of reduced coenzyme Q_{10} at a site containing a non-heme iron protein (MW ≈ 16000). Chloroquine does not, however, inhibit the oxidation of durohydroquinone; this finding is consistent with chloroquine competition for enzyme sites with CoQ_{10}.

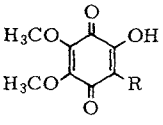
Other important evidence, although indirect, for the inhibition of coenzyme Q systems by antimalarial naphthoquinones was found in a study of the changes in *P. berghei* fine structure induced by menoctone *(13)* and primaquine *(4)*[33]. The initial mitochondrial swelling would appear to be followed by generalized degenerative changes in the plasmodia. This finding suggested an initial action of the drugs on the parasite's mitochondria, the apparent CoQ_8-containing organelle in which oxidative processes are carried out.

In a study of chloroquine resistance in malaria by *Fitch*[34], the major difference between chloroquine-sensitive and chloroquine-resistant parasites was a deficiency of high affinity binding of chloroquine by cells infected with the chloroquine-resistant parasite. This binding deficiency could explain the reduced ability of chloroquine-resistant parasites to concentrate chloroquine[35, 36] and suggests that chloroquine-resistance is due to a decrease in the number, affinity, or accessibility of chloroquine receptor sites in the malaria parasite.

6. Synthesis of Other Antimetabolites of Coenzyme Q

At this stage of the investigations, the synthesis of new quinones as potential antimalarials could be designed upon new knowledge of the existence and role of coenzyme Q_8 in the metabolism of plasmodia.

New hydroxybenzoquinones based on the structure of coenzyme Q, the 2-alkyl-3-hydroxy-5,6-dimethoxy-1,4-benzoquinones *(14)*, were synthesized by *Catlin et al.*[37,38] by procedures which permitted considerable structural variation; the alkyl groups were aliphatic (including isoprenoid moieties). *Catlin et al.*[37,38] and *Pardini et al.*[39] found the quinones *(14)* to be potent inhibitors of coenzyme Q enzyme systems. *In vitro* studies showed that some of these hydroxy-1,4-benzoquinones strongly inhibit succinate-dehydrogenase and NADH-



(14)

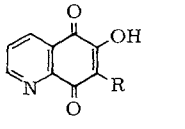
dehydrogenase in intact mitochondrial systems from bovine heart (Table 1)[37] or in a system which is extracted for removal of coenzyme Q_{10}[37]. Compound *(14c)* was more effective than other phytyl derivatives carrying residues other than OH[39]. The succinate-dehydrogenase system was generally more sensitive to most of the benzoquinones than was the NADH-dehydrogenase system, the influence of the alkyl side chains on the activity being very slight[39].

According to *Castelli et al.*[40] the quinones *(14a)* and *(14c)* are also effective inhibitors of NADH- and succinate-dehydrogenase of intact mitochondria from yeast. CoQ_2 reversed the inhibition in NADH-dehydrogenase, but there was little or no significant reversal in succinate-dehydrogenase. Surprisingly, when CoQ_6-deficient NADH-dehydrogenase was supplemented with 2-hydroxy-5,6-dimethoxy-3-phytyl-1,4-benzoquinone *(14c)* and CoQ_{10}, there was an unexpected increase in enzyme activity, indicating some coenzymatic activity in this particular case[40].

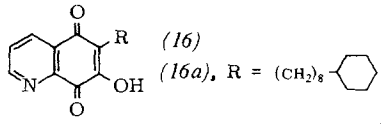
It is important to emphasize that the coenzyme Q_8 of plasmodia is a lipoidal substance; this is largely because of the forty carbon atoms in its isoprenoid side chain. Consequently, one may presume that effective inhibitors of coenzyme Q_8 would, of necessity, also have to be lipoidal in nature. For this reason, the synthesis of several categories of lipoidal quinones has been undertaken as part of our research toward new and effective prophylactic and curative antimalarials. Quinones were designed with long side chains to impart lipoid character and with various ring substituents which could offer differences in oxidation-reduction potentials, hydrogen bonding, and alkylation sites.

6.1. Alkylhydroxyquinolinequinones

Two series of lipoidal quinones which were examined in this connection were the 7-alkyl-6-hydroxy- and 6-alkyl-7-hydroxy-5,8-quinolinequinones *(15)* and *(16)*, respectively, which had previously already been synthesized by *Pratt* and *Drake*[41,42]. In this study, *Porter et al.*[43] synthesized additional new alkylated 5,8-quinolinequinones, namely by alkylation of 6- and 7-hydroxy-5,8-quinolinequinones, with diacyl peroxides.



(15)



(16)

(16a), R = $(CH_2)_8$-⬡

In the 7-alkyl-6-hydroxy-5,8-quinolinequinone series *(15)*, maximum antimalarial activity against blood-induced *P. berghei* in mice, according to the procedure of *Osdene et al.*[44], was displayed by compound *(15a)* with a side chain of 15 carbon atoms. 6-Hydroxy-7-*n*-pentadecyl-5,8-quinolinequinone *(15a)*[43] showed 1/5 cures and an extension of survival time (T − C) = 13.2 days at 640 mg/kg in the routine one-dose treatment (sc) of mice infected with *P. berghei*. In the 6-alkyl-7-hydroxy-5,8-quinolinequinone *(16)* series, 6-(8-cyclohexyloctyl)-7-hydroxy-5,8-quinolinequinone *(16a)* was the most potent antimalarial; it effected 5/5 cures at 640 mg/kg under the same test conditions.

Most of the 7-alkyl-6-hydroxy-5,8-quinolinequinones *(15)* were also tested on NADH-dehydrogenase and succinate-dehydrogenase in bovine heart mitochondria for inhibition of coenzyme Q[45] (see Table 2). The results demonstrated that a reasonably good correlation existed in this series of quinones between the concentration of the inhibitor in the *in vitro* system and the observed *in vivo* antimalarial activity against *P. berghei* in mice. In succinate-dehydrogenase, the greatest inhibitions were found in the case of analogs with 7-*n*-tetradecyl- *(15e)*, 7-*n*-pentadecyl- *(15f)*, 7-*n*-hexadecyl- *(15g)*, 7-(5-cyclohexylpentyl)- *(15k)*, and 7-(8-cyclohexyloctyl)- *(15l)* side chains. NADH-dehydrogenase was less sensitive than succinate-dehydrogenase to these analogs; *(15f)*,

Table 1. *In-vitro* assay of the inhibitory activity of some 2-alkyl-3-hydroxy-5,6-dimethoxy-1,4-benzoquinones *(14)* [a] on NADH-dehydrogenase- and succinate-dehydrogenase-enzyme systems in intact mitochondrial systems. The specific activity (S.A.) is defined as the oxygen uptake in μatoms O_2/min per milligram of mitochondrial protein.

Addition to enzyme system	NADH-dehydrogenase S.A.		S.A.		Succinate-dehydrogenase S.A.		S.A.	
	abs.	[%]	abs.	[%]	abs.	[%]	abs.	[%]
None	0.396	65	0.406	50	0.452	85	0.366	80
CoQ_{10}	0.596	100	0.794	100	0.533	100	0.445	100
CoQ_{10} + *(14a)*, R = Farnesyl			0.608	75	0.309	60		
CoQ_{10} + *(14b)*, R = Solanesyl	0.364	60			0.164	30		
CoQ_{10} + *(14c)*, R = Phytyl							0.129	30
CoQ_{10} + *(14d)*, R = Dihydrophytyl	0.302	50					0.096	20
CoQ_{10} + *(14e)*, R = *n*-$C_{10}H_{39}$	0.316	50			0.117	20		

[a] Addition in each case was 100 nmol of the quinones.

Table 2. Inhibitory activity of 7-alkyl-6-hydroxy-5,8-quinolinequinones *(15)* on the NADH-dehydrogenase-CoQ and succinate-dehydrogenase-CoQ enzyme systems. The specific activity (S.A.) is defined as the oxygen uptake in µatoms O_2/min per 1 mg mitochondrial protein.

Cpd.	R.	NADH-dehydrogenase				Succinate-dehydrogenase			
		Conc. [a]	S.A.	Inhibition [%]	AI_{50} [b]	Conc. [a]	S.A.	Inhibition [%]	AI_{50} [b]
		---	0.49	---	---	---	0.47	---	---
(15a)	n-C_5H_{11}	190	0.50	---	> 100	230	0.39	15	> 100
(15b)	n-C_8H_{17}	19	0.37	26		16	0.28	40	
		32	0.25	50	16	20	0.25	48	
						22	0.19	60	
						27	0.070	80	9.5
(15c)	n-$C_{10}H_{21}$	2.5	0.41	17		2.2	0.31	34	
		4.2	0.28	44		2.7	0.22	53	
		5.1	0.17	66	2.2	5.5	0.047	90	1.3
(15d)	n-$C_{13}H_{27}$	4.2	0.25	50		2.7	0.34	26	
		5.1	0.14	71	2.1	3.6	0.22	54	
						3.8	0.27	41	
						4.4	0.092	80	
						5.7	0.027	90	1.7
(15e)	n-$C_{14}H_{29}$	3.2	0.24	51	1.6	2.2	0.24	40	1.1 [d]
(15f)	n-$C_{15}H_{31}$	2.5	0.22	56	1.3 [c]	0.82	0.34	28	
						1.4	0.29	40	
						1.6	0.171	63	0.75
(15g)	n-$C_{16}H_{33}$	1.9	0.31	38		1.1	0.29	40	
		3.2	0.19	58		1.4	0.20	58	
		6.4	0.085	83	1.4	1.6	0.17	64	0.65
(15h)	n-$C_{19}H_{39}$	2.9	0.32	35					
		3.6	0.20	60	1.7	2.7	0.23	50	1.4
(15i)	CH_2-c-C_6H_{11}	190	0.33	33	> 100	160	0.34	28	> 80
(15j)	$(CH_2)_3$-c-C_6H_{11}	38	0.31	38					
		45	0.28	43		22	0.25	47	
		64	0.20	60	27	27	0.091	80	1.1
(15k)	$(CH_2)_5$-c-C_6H_{11}	2.5	0.27	46	1.3	1.6	0.29	38	
						2.1	0.17	64	0.9
(15l)	$(CH_2)_8$-c-C_6H_{11}	3.8	0.24	51					
		4.5	0.22	56		2.2	0.25	46	
		5.1	0.16	77	1.9	4.4	0.012	97	1.2

[a] nmol inhibitor/mg mitochondrial protein.
[b] Antimetabolite-CoQ_{10} index: for a definition see Section 7. The average concentration of CoQ_{10} in mitochondria was determined from several preparations of mitochondria and found to be *ca.* 2 nmol/mg mitochondrial protein. This value was assumed for the calculation of AI_{50}.
[c] For 56% inhibition.
[d] For 40% inhibition.

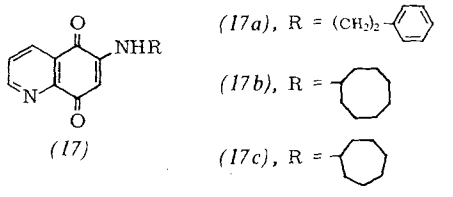
(15g), and *(15k)* analogs were the most inhibitory. For both *in vitro* enzyme systems, the optimum length of the lipoidal straight side chain for maximum inhibition was 15 or 16 carbon atoms.

Skelton et al.[46] found that menoctone *(13)* and a representative of the 5,8-quinolinequinones, 7-(8-cyclohexyloctyl)-6-hydroxy-5,8-quinolinequinone *(15l)*, inhibit succinate-cytochrome c reductase and the succinate-coenzyme Q reductase in bovine heart submitochondrial systems and that coenzyme Q_6 effects reversal of inhibition. The same substances also inhibit the succinate-coenzyme Q reductase of intact mitochondria from the human heart.

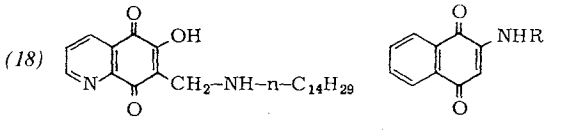
In another study, *Skelton et al.*[47] attempted elucidation of the mechanism of action of these quinone antimalarials. Menoctone *(13)* and the quinolinequinone *(15l)* inhibited the NADH-cytochrome c reductase system of yeast submitochondrial particles and the succinate-cytochrome c reductase systems of both yeast and bovine heart submitochondrial fragments[47]. The inhibition could be reversed by addition of exogenous coenzyme Q_6 to the systems containing no added phospholipid[47]. Lineweaver-Burk double reciprocal plots indicated that these two quinones act by competitive inhibition of coenzyme Q enzyme systems[47].

6.2. Alkylamino-quinolinequinones and -naphthoquinones

Other categories of quinones newly synthesized as potential antimalarials are 6-alkylamino-5,8-quinolinequinones *(17)*, 6-hydroxy-7-*n*-tetradecylaminomethyl-5,8-quinolinequinone *(18)*, and the 2-alkylamino-1,4-naphthoquinones *(19)*. Numerous quinones of this type have already been reported[41,42,48–50].



(17)



It was important to design these new quinone types with alkyl side chains, so as to impart greater lipoidal character to the molecule, and with alkyl side chains containing varying types and numbers of heteroatoms. It was hoped that such analogs might be more effective antimetabolites of the highly lipoidal coenzyme Q_8 of plasmodia.

A series of fifteen new 6-alkylamino-5,8-quinolinequinones *(17)* and 6-hydroxy-7-*n*-tetradecylaminomethyl-5,8-quinolinequinone *(18)* were synthesized by *Porter et al.*[51], and representative compounds were evaluated for antimalarial activity against *P. berghei* in mice[44]. Three quinones 6-phenethylamino-5,8-quinolinequinone *(17a)* (T–C = 7.3

at 640 mg/kg), 6-cyclooctylamino-5,8-quinolinequinone *(17b)* (T − C = 6.9 at 640 mg/kg), and 6-cycloheptylamino-5,8-quinolinequinone *(17c)* (T − C = 6.5 at 320 mg/kg)—were declared "active" by the standard criterion of 100% increase or greater in the survival time for antimalarial activity against *P. berghei*; all three derivatives were non-toxic at the dose levels tested.

Representative compounds were tested in mitochondrial NADH-dehydrogenase and succinate-dehydrogenase systems for inhibition of coenzyme Q. The 6-alkylamino-5,8-quinolinequinones *(17)*, represented in the assay by seven of the fifteen compounds, were potent inhibitors in both the NADH-dehydrogenase and succinate-dehydrogenase systems; the inhibition could be completely reversed by CoQ_{10} (see Table 3)[51].

Eight new 2-alkylamino-1,4-naphthoquinones, *(19)*, have also been synthesized by *Porter et al.*[52] and tested for antimalarial activity against *P. berghei* in mice. None of these compounds, however, showed any significant activity in this test. Significantly, the 2-alkylamino-1,4-naphthoquinones, represented in the *in vitro* assay by seven of the eight new compounds and three previously prepared derivatives, likewise showed no important inhibition of either the NADH- or succinate-dehydrogenase enzyme system[52].

Table 4. *In-vivo* assay of antimalarial activity of 7-alkylthio-5,8-quinolinequinones *(20)* [a] on mice infected with *P. berghei* [44]. The figures in brackets denote the dose (in mg/kg) administered in each case.

Cpd.	R	(T − C) [b]	Cures	Deaths
(20a)	n-$C_{12}H_{25}$	13.9 (320)	0/5 (320)	0/5 (320)
(20b)	n-$C_{14}H_{29}$	3.7 (160)	0/5 (160)	0/5 (160)
(20c)	n-$C_{16}H_{33}$	5.9 (20)	2/5 (80)	0/5 (80)
		17.9 (160)	3/5 (160)	0/5 (160)
(20d)	n-$C_{18}H_{37}$	7.9 (80)	5/5 (320)	0/5 (320)
		9.5 (160)	5/5 (640)	0/5 (640)
(20e)	n-$C_{22}H_{45}$	0.1 (160)	0/5 (160)	0/5 (160)
(20f)	$(CH_2)_6$-c-C_6H_{11}	2.7 (160)	0/5 (160)	0/5 (160)
(20g)	$C_{17}H_{35}$	10.9 (80)	0/5 (80)	0/5 (80)

[a] All compounds were administered subcutaneously, in graded doses, to groups of five mice.
[b] T − C = change in survival time, in days, of treated (T) and untreated animals (C = control).

hydroquinones. These quinones were tested for antimalarial activity against *P. berghei* in mice[44]. Of the seven compounds tested to date, five showed marked *in vivo* antimalarial activity without apparent toxicity (Table 4).

6-Hydroxy-7-*n*-octadecylthio-5,8-quinolinequinone *(20d)* was active at 80 mg/kg and totally curative (5/5 cures) at

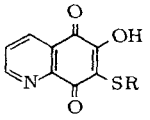
Table 3. *In-vitro* assay of the inhibition of coenzyme-Q enzyme systems by 6-alkylamino-5,8-quinolinequinones *(17)* [a] (after Ref. [31]). The specific activity (S.A.) is defined as the oxygen uptake in μatoms O_2/min per 1 mg of mitochondrial protein.

Cpd.	R	NADH-dehydrogenase S.A.	NADH-dehydrogenase Conc. [b]	NADH-dehydrogenase Reversal [%] [c]	Succinate-dehydrogenase S.A.	Succinate-dehydrogenase Conc. [b]
CoQ_{10}		0.582			0.562	
(17d)	n-C_4H_9	0.302	41	90	0.292	15
(17e)	n-$C_{10}H_{21}$	0.321	17	97	0.288	10
(17f)	n-$C_{14}H_{29}$	0.320	17	98	0.286	11
(17g)	n-$C_{15}H_{31}$	0.328	20	95	0.290	10
(17h)	n-$C_{16}H_{33}$	0.326	20	95	0.288	10
(17i)	$(CH_2)_3N(n\text{-}C_4H_9)_2$	0.318	14	98	0.290	9
(17j)	$(CH_2)_4$-c-C_6H_{11}	0.320	17	98	0.291	10

[a] Addition of 100 nmol CoQ_{10} in each case.
[b] For 50% inhibition. The concentration of inhibitor is given in nmol/mg mitochondrial protein.
[c] After further addition of 200 nmol CoQ_{10}.

6.3. Alkylthiohydroxyquinolinequinones

One of our most recent series of quinones, the 7-alkylthio-6-hydroxy-5,8-quinolinequinones *(20)* described by *Porter et al.*[53], represent a new structural type of effective antimalarial quinones, which show little or no toxicity in the prophylactic assays, and which most likely function as antimetabolites of the indispensible coenzyme Q_8 of plasmodia. This series of new antimetabolites of coenzyme Q appears to be one of the most promising types of such analogs in our research on the prophylactic and curative treatment of malaria.

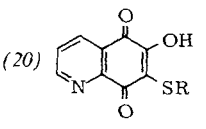


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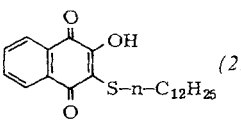
Twelve new 7-alkylthio-6-hydroxy-5,8-quinolinequinones *(20)* were synthesized by *Porter et al.*[53] and *Wan et al.*[54] by 1,4-addition of appropriate alkanethiols to 6-hydroxy-5,8-quinolinequinone and subsequent oxidation of the quinoline-

dose levels of both 320 mg/kg and 640 mg/kg without toxicity in the routine one-dose (sc) treatment of mice.

Prophylactically, this compound cured 3/5 chicks at 160 mg/kg (Table 5) in the sporozoite-induced *P. gallinaceum* test developed by *Rane* and *Rane*[55]. 6-Hydroxy-7-oleylthio-5,8-quinolinequinone *(20h)*, the corresponding C_{18} derivative having one double bond in the side chain, showed increased *in vivo* prophylactic activity with 4/5 cures at 15 mg/kg. In comparison, compound *(20d)* showed only 1/5 cures at 40 mg/kg. Unsaturation in the side chains appears to enhance *in vivo* prophylactic activity. The lower homolog of *(20d)*, 6-hydroxy-7-*n*-tetradecylthio-5,8-quinolinequinone *(20b)*, was totally curative[23], curing 5/5 chicks at a dose of 80 mg/kg. The best compound, 7-*n*-heptadecylthio-6-hydroxy-5,8-quinolinequinone *(20g)*, cured 5/5 chicks at a dose of 10 mg/kg; its effectiveness at



(20)



(21)

Table 5. *In-vivo* assay of the antimalarial activity of 7-alkylthio-5,8-quinolinequinones *(20)* [a] on chickens infected with sporozoites of *P. gallinaceum* [55]. The figures given in brackets denote the dose (in mg/kg) administered in each case.

Cpd.	R	(T – C) [b]	Cures	Deaths
(20d)	n-$C_{18}H_{37}$	3.5 (40)	1/5 (40)	0/5 (40)
		1.7 (80)	2/5 (80)	0/5 (80)
		1.7 (160)	3/5 (160)	1/5 (160)
			3/5 (320)	2/5 (320)
(20b)	n-$C_{14}H_{29}$	7.6 (20)	4/5 (20)	0/5 (20)
			5/5 (80)	0/5 (80)
			5/5 (320)	0/5 (320)
(20g)	n-$C_{17}H_{35}$		5/5 (10)	0/5 (10)
			5/5 (40)	0/5 (40)
			5/5 (320)	0/5 (320)
(20c)	n-$C_{16}H_{31}$		5/5 (120)	0/5 (120)
			5/5 (240)	0/5 (240)
			5/5 (480)	0/5 (480)
(20h)	$(CH_2)_8CH{=}CH(CH_2)_7CH_3$ [c]	9.9 (15)	4/5 (15)	0/5 (15)
		9.9 (30)	4/5 (30)	0/5 (30)
			5/5 (60)	0/5 (60)
			5/5 (120)	0/5 (120)
(20i)	n-$C_{19}H_{39}$	0.3 (15)	2/5	
		1.8 (120)	5/5 (120)	0/5 (120)
			5/5 (240)	0/5 (240)
			5/5 (480)	0/5 (480)

[a] All compounds were administered subcutaneously to groups of five mice.
[b] T – C = change in survival time, in days, of treated and nontreated (control) animals.
[c] This compound was declared "active" at this dose level by the standard of 100% increase in survival time.

lower dosages is as yet unknown. This quinone showed no toxicity at doses from 10 mg/kg to 320 mg/kg.

The alkylthio-5,8-quinolinequinones *(20a)*, *(20c)*, and *(20d)* and the alkylthio-1,4-naphthoquinone *(21)* showed marked inhibition of both NADH- and succinate-dehydrogenase mitochondrial CoQ-enzyme systems from bovine heart (Table 6).

6-Hydroxy-7-*n*-octadecylthio-5,8-quinolinequinone *(20d)*, the quinolinequinone which exhibited the greatest *in vivo* activity against *P. berghei* in the mouse, showed more inhibitory activity in the NADH-dehydrogenase system than the other two alkylthio-5,8-quinolinequinones *(20a)* and *(20c)* tested in the same assay. Surprisingly, 2-*n*-dodecylthio-3-hydroxy-1,4-naphthoquinone *(21)*, which showed only marginal antimalarial activity in the murine assay, was a potent inhibitor of the mitochondrial NADH- and succinate-dehydrogenase enzyme systems.

The effectiveness of these alkylthio-5,8-quinolinequinones, *in vitro* and *in vivo*, may be due to their having a combination of molecular characteristics for inhibition including electron transport, relative affinities for binding to functional and/or biosynthetic sites of CoQ_8 in plasmodia, and lipoidal character.

The screening results[27] described herein for mice[44] and chicks[55] are generally based on findings which were obtained on treatment of animals with only one dose; this method was chosen for simplicity of routine assay of very large numbers of compounds. It is not known what the dosage and drug

Table 6. *In-vitro* assay of the inhibitory activity of some 7-alkylthio-5,8-quinolinequinones *(20)* and of a 1,4-naphthoquinone compound *(21)* on the CoQ enzyme systems NADH-dehydrogenase and succinate-dehydrogenase. The specific activity (S.A.) is defined as the oxygen uptake in µatoms O_2/min per 1 mg of mitochondrial protein. Reaction mixture contained no exogenous coenzyme Q.

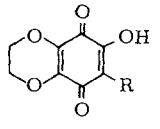
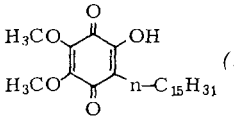
Cpd.	R	NADH-dehydrogenase S.A.	NADH-dehydrogenase Conc. [a]	NADH-dehydrogenase Inhibition [%]	Succinate-dehydrogenase S.A.	Succinate-dehydrogenase Conc. [a]	Succinate-dehydrogenase Inhibition [%]
(20a)	n-$C_{12}H_{25}$	0.31	0	0	0.30	0	0
		0.26	26	16	0.20	17	35
		0.12	51	63	0.14	26	88
		0.074	64	76	0.13	34	57
(20c)	n-$C_{16}H_{33}$	0.31	0	0	0.30	0	0
		0.27	13	15	0.19	13	36
		0.21	19	33	0.15	17	52
		0.079	26	75	0.17	19	45
		0	32	100	0.12	20	59
					0.10	20	66
(20d)	n-$C_{18}H_{37}$	0.31	0	0	0.30	0	0
		0.22	13	30	0.23	8.5	24
		0.18	16	41	0.21	13	30
		0.12	19	61	0.13	17	56
					0.15	17	52
(21)		0.31	0	0	0.32	0	0
		0.21	13	33	0.24	8.5	20
		0.16	13	48	0.14	13	53
		0.054	20	83	0.19	13	37

[a] nmol of inhibitor/mg mitochondrial protein.

effectiveness would be if the optimum regimen were determined by the traditional procedures of pharmacology in the case of the most promising antimetabolites of coenzyme Q for antimalarial effectiveness.

6.4. Benzodioxinquinones (Ethylenedioxyquinones)

A new series of coenzyme Q analogs, the 6-alkyl-7-hydroxy-2,3-dihydro-1,4-benzodioxin-5,8-quinones (ethylenedioxybenzoquinones) *(22)*, have been synthesized by *Bowman et al.*[56] on the basis of the minor differences in the electronic and rotational nature between the ethylenedioxy group and the two methoxy groups. These differences could fundamentally affect the oxidation-reduction potential of the 1,4-benzoquinone and, in turn, also the inhibitory activity. Appropriate isoprenyl or alkyl groups were inserted at C-6 by alkylation.

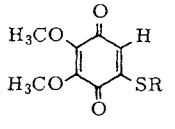
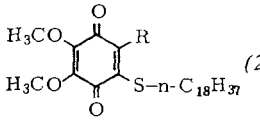
(22)   *(14f)*

The succinate-dehydrogenase and NADH-dehydrogenase systems of intact mitochondria from bovine heart were used in tests for inhibition of these quinones *in vitro* (Table 7). In succinate-dehydrogenase the *n*-nonyl *(22a)*, *n*-decyl *(22b)*, *n*-pentadecyl *(22d)*, and farnesyl *(22g)* derivatives showed inhibitions of less than 40%; the phytyl *(22f)*, *n*-heptadecyl *(22e)*, and 5-cyclohexylpentyl *(22c)* analogs showed inhibitions of about 50%. All analogs were less inhibitory in NADH-dehydrogenase.

2-Hydroxy-5,6-dimethoxy-3-*n*-pentadecyl-1,4-benzoquinone *(14f)* and the analogous compound *(22d)* showed about 90% and 35% inhibition, respectively, in succinate-dehydrogenase—the strongest inhibitions in this series of experiments. Apparently, the dimethoxy groups are more favorable than the ethylenedioxy group for the inhibition of enzymes.

6.5. Alkylthio-2,3-dimethoxy-1,4-benzoquinones

Another new category of 2-alkylthio-5,6-dimethoxy-1,4-benzoquinones, compounds *(23)* and *(24)*, have recently been synthesized by *Wikholm et al.*[57] as potential antimetabolites of coenzyme Q.

(23)  *(24)* 

(23a), R = *n*-$C_{12}H_{25}$
(23b), R = *n*-$C_{18}H_{37}$
(23c), R = phytyl

(24a), R = Cl
(24b), R = NH_2
(24c), R = $C_{18}H_{37}$

The series of alkylthio-1,4-benzoquinones prepared in this study provided variation in alkyl side chain length; in addition one compound having a branched alkenylthio substituent [*(23c)*] was also prepared. Within the series of 2,3-dimethoxy-5-*n*-octadecylthio-1,4-benzoquinones *(24)* several 6-substituents provided potentially significant variation in redox potential of the new quinones.

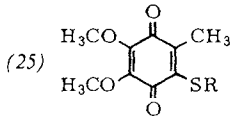
In the 6-substituted 2,3-dimethoxy-5-methyl-1,4-benzoquinone *(25)*, lengthening of the alkylthio side chain—from

Table 7. *In-vitro* assay of the inhibitory activity of benzodioxinquinones *(22)* and dimethoxybenzoquinone *(14f)* on NADH-dehydrogenase and succinate-dehydrogenase in intact mitochondrial systems.

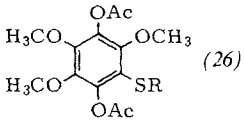
Cpd.	R	NADH-dehydrogenase Conc. [a]	NADH-dehydrogenase Inhibition [%] [b]	Succinate-dehydrogenase Conc. [a]	Succinate-dehydrogenase Inhibition [%] [b]
(22a)	*n*-C_9H_{19}	120	22	67	10
		180	24	130	24
				200	24
(22b)	*n*-$C_{10}H_{21}$	100	26	125	21
		150	35	170	30
				250	34
(22c)	$(CH_2)_5$-c-C_6H_{11}	100	26	50	22
		150	45	115	40
				150	60
(22d)	*n*-$C_{15}H_{31}$	100	34	100	30
		205	35	140	37
				205	37
(22e)	*n*-$C_{17}H_{35}$	60	25	60	29
		100	37	120	45
		130	33	180	50
(22f)	Phytyl	64	22	64	34
		130	43	190	45
		190	59		
(22g)	Farnesyl	130	0	130	23
		190	10	190	24
(14f)		32	61	32	72
		65	72	65	86
		130	74	97	91
		190	79	205	90

[a] Concentration of inhibitor is expressed in nmol/mg of mitochondrial protein.
[b] Activity of the enzyme system was determined in microatoms of oxygen uptake per minute per milligram protein. The percent inhibition is equivalent to: (specific activity of test system/specific activity of control system) × 100%. The general methodology has been described [31].

the *n*-dodecylthio- to the *n*-octadecylthio group—furnished coenzyme Q analogs with increasing lipoidal character.



(25)



(26)

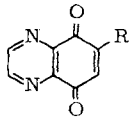
(25a), R = $C_{12}H_{25}$
(25b), R = $C_{14}H_{29}$
(25c), R = $C_{18}H_{37}$

(26a), R = $C_{12}H_{25}$
(26b), R = $C_{18}H_{37}$

Finally, reductive acetylation of crude 2-alkylthio-3,5,6-trimethoxy-1,4-benzoquinone, another analog in this series, afforded the crystalline diacetoxy derivatives *(26)* of the corresponding hydroquinones.

6.6. Alkylquinoxalinequinones

Recently, *Porter et al.*[58] have initiated the synthesis of a new series of 6-alkyl-5,8-quinoxalinequinones *(27)*, and the alkylthioquinones were investigated as potential inhibitors of



(27a), R = S-n-$C_{12}H_{25}$

(27b), R = $(CH_2)_5$-⬡

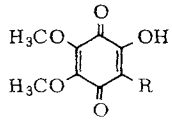
coenzyme Q and as antimalarial drugs. The groups introduced as side chains were *n*-dodecylthio- *(27a)* and 5-cyclohexylpentyl- *(27b)*. *(27a)* was inactive against blood-induced *P. berghei* in mice at 640 mg/kg and inactive against sporozoite-induced *P. gallinaceum* in chicks at 80 mg/kg.

(28a) has been tested prophylactically against sporozoite-induced *P. gallinaceum* in the chick and was effective, without toxicity, at dose levels of 30 mg/kg (1/5 cures) and 120 mg/kg (4/5 cures).

7. Comparison of Inhibitory Activity by the Antimetabolite CoQ_{10} Index (AI_{50})

To facilitate comparison of the inhibitory activities of various analogs and derivatives *in vitro*, *Bowman et al.*[45] have defined an "antimetabolite CoQ_{10} index" (AI_{50}); this corresponds to the ratio of nmoles of analog per nmoles of CoQ_{10} in the actual mitochondrial preparation which causes approximately 50% inhibition of enzyme activity. The inhibitory activities of these analogs were measured by their effect on the oxygen uptake of the CoQ enzymes (determined either by the Warburg manometric method or by polarographic measurement of oxygen). For most analogs, inhibition of the CoQ enzymes was determined at several concentrations so that the concentration at which 50% inhibition was effected could be estimated by extrapolation.

The antimetabolite CoQ_{10} indices for some 7-alkyl-6-hydroxy-5,8-quinolinequinones *(15)* in NADH-dehydrogenase and succinate-dehydrogenase are listed in Table 2[45]. The 7-*n*-pentadecyl- and 7-(5-cyclohexylpentyl)-6-hydroxy-5,8-quinolinequinones *(15f)* and *(15k)* were the most effective antimetabolites of this series in NADH- and succinate-dehydrogenase.



(14)

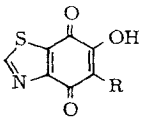
Table 8. Antimetabolite CoQ_{10} indices of 2-alkyl-3-hydroxy-5,6-dimethoxy-1,4-benzoquinones *(14)*.

Cpd.	R	NADH-dehydrogenase AI_{50}	NADH-dehydrogenase Inhibition [%] [a]	Succinate-dehydrogenase AI_{50}	Succinate-dehydrogenase Inhibition [%] [a]
(14g)	n-$C_{10}H_{21}$	9	50	7.7	50
(14h)	$(CH_2)_5$-c-C_6H_{11}	5	57	5.5	50
(14i)	n-$C_{14}H_{29}$	10	48	8	50
(14f)	n-$C_{15}H_{31}$	10	50	7	50
(14e)	n-$C_{19}H_{39}$	32	50	8	50
(14j)	n-$C_{21}H_{43}$	11	48	14	50
(14a)	Farnesyl	17	50	10	50
(14c)	Phytyl	26	50	10	50

[a] Actual 50% inhibitions or approximately 50% inhibitions from extrapolation of experimental values [45].

6.7. Benzothiazolequinones

A new series of 5-alkyl-6-hydroxybenzothiazole-4,7-quinones *(28)* have been synthesized by *Friedman et al.*[59] in the continuing program to explore new heterobicyclic quinone systems for potential pharmacological activity. The two new quinones *(28a)* and *(28b)*, containing *n*-undecyl and *n*-pentadecyl side chains, respectively, were prepared by a multistep procedure.



(28a), R = n-$C_{11}H_{21}$

(28b), R = n-$C_{15}H_{31}$

The antimetabolite CoQ_{10} indices of eight 2-alkyl-3-hydroxy-5,6-dimethoxy-1,4-benzoquinones *(14)* have been determined by *Bogentoft, von Klaudy*, and *Folkers*[60] (Table 8). For the CoQ-NADH-dehydrogenase system, a range of antimetabolite indices of 5—32 were obtained for these inhibitors. The 2-(5-cyclohexylpentyl)-analog *(14h)* was the most effective antimetabolite with an index of 5. The farnesyl- and phytyl-analogs *(14a)* and *(14c)* had indices of 17 and 26, respectively. The antimetabolite CoQ_{10} indices for the CoQ-succinate-dehydrogenase system varied from 5.5 to 14 for all eight analogs;

no difference was evident in the case of the farnesyl and phytyl derivatives.

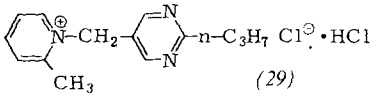
In general, these eight analogs were more effective antimetabolites of CoQ in succinate-dehydrogenase than in NADH-dehydrogenase, but the difference in sensitivity between the two systems was small.

8. Application of Coenzyme Q Antimetabolites in the Therapy of Other Diseases

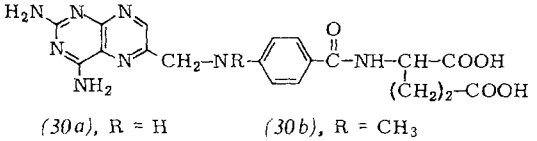
This demonstrated effectiveness, both curatively and prophylactically, of antimetabolites of coenzyme Q in the treatment of malaria, with little or no toxicity, may be extended to the therapy of other diseases. From the above data it can be concluded that a certain selective toxicity for an antimetabolite of CoQ has been achieved and that further analogs can be synthesized which could exhibit even more effective selective toxicity in chemotherapy. Such selective toxicity can be based on differential inhibition of pathways. The widespread occurrence of coenzyme Q in nature would suggest its presence in a number of potential pathogens such as bacteria, fungi, other protozoa, and helminths. Antimetabolites of coenzyme Q could destroy these organisms or inhibit their growth.

The criticism is frequently encountered that an antimetabolite of a vitamin cannot be useful in man or domestic animals without serious toxicity to the host, which negates the useful aspect. Evidence shows that such toxicity to the host does not necessarily occur. Moreover, the progress described here on antimetabolites of coenzyme Q demonstrates that useful therapeutic activity without toxicity is feasible.

Antimetabolites or other vitamins are already in use in the treatment of diseases. Amprolium *(29)*[61], a thiamine antagonist, is suitable as a coccidiostat in veterinary medicine; it is selectively effective against coccidia of the digestive tract and prevents coccidiosis in chickens without adverse effect upon growth.



(29)



(30a), R = H *(30b)*, R = CH_3

Similarly, antifolates have found widespread application in the treatment of cancer because of their selective toxicities. The folic acid antagonists aminopterin *(30a)* and methotrexate *(30b)*, are both used in the treatment of acute leukemia in children[62].

Appreciation is particularly expressed to Dr. David P. Jacobus for his sympathetic encouragement of the initiation of the basic research which led to the establishment of coenzyme Q_8 as intrinsic to the metabolism of plasmodia. For their subsequent cooperation we wish to thank Dr. Thomas R. Sweeney and Dr. Edgar A. Steck of the U.S. Army Medical Research and Development Command (Contract No. DADA 17-69-C-9067); Contribution No. 1202 from the Army Research Program on malaria. We also wish to express our thanks to the Robert A. Welch Foundation, and Dr. Lewis H. Sarett, Merck Sharp and Dohme Research Laboratories, New Jersey, for their valuable support of this work.

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[1] *E. A. Steck:* The Chemotherapy of Protozoan Disease. Division of Medicinal Chemistry, Walter Reed Army Institute of Research, 1971. Vol. 3, p. 23.

[2] *K. Folkers:* Chemistry of Natural Products. Division of Organic Chemistry, International Symposium, Stockholm 1966. Vol. 4, p. 7.

[3] *R. D. Powell, G. J. Brewer, A. S. Alving,* and *J. W. Millar,* Bull. WHO *30*, 29 (1964).

[4] *R. D. Powell, G. J. Brewer, A. S. Alving,* and *J. W. Millar,* Bull. WHO *31*, 379 (1964).

[5] *A. Bishop,* Parasitology *57*, 755 (1967).

[6] *L. F. Fieser, E. Berlinger, F. J. Bondhus, F. C. Chang, W. G. Dauber, M. G. Ettlinger, G. Fawaz, M. Fields, M. Fieser, C. Heidelberger, H. Heymann, A. M. Seligman, W. R. Vaughan, A. G. Wilson, E. Wilson, M. Wu, M. T. Leffler, K. E. Hamlin, R. J. Hathaway, E. J. Matson, E. E. Moore, M. B. Moore, R. T. Rapald,* and *H. E. Zaugg,* J. Amer. Chem. Soc. *70*, 3151 (1948).

[7] *L. F. Fieser,* and *H. Heymann,* J. Biol. Chem. *176*, 1363 (1948).

[8] *F. Y. Wiselogle:* Survey of Antimalarial Drugs 1941–1945. Edwards, Ann Arbor 1946.

[9] *D. H. Clarke* and *M. Theiler,* J. Infect. Dis. *82*, 138 (1948).

[10] *L. Whitman,* J. Infect. Dis. *82*, 251 (1948).

[11] *W. B. Wendell,* Fed. Proc. *5*, 406 (1946).

[12] *C. C. Smith, R. Fradkin,* and *M. D. Lackey,* Proc. Soc. Exp. Biol. Med. *61*, 398 (1946).

[13] *C. C. Smith, R. Fradkin,* and *M. D. Lackey,* Proc. Soc. Exp. Biol. Med. *64*, 45 (1947).

[14] *K. Folkers, C. H. Shunk, B. O. Linn, N. R. Trenner, D. E. Wolf, C. H. Hoffman, A. C. Page, Jr.,* and *F. R. Koniuszy:* Quinones in Electron Transport, Ciba Foundation Symposium, Little, Brown and Co., Boston 1961, p. 100.

[15] *D. Hendlin* and *T. M. Cook,* Biochem. Biophys. Res. Commun. *2*, 71 (1960).

[16] *S. Takemari* and *T. E. King,* J. Biol. Chem. *239*, 3546 (1964).

[17] *J. L. Howland,* Biochim. Biophys. Acta *105*, 205 (1965).

[18] *M. A. Rudzinska* and *W. Trager,* J. Protozool. *4*, 190 (1957).

[19] *P. K. Hepler, C. G. Huff,* and *H. Spring,* J. Cell Biol. *30*, 333 (1966).

[20] *P. J. Rietz, F. S. Skelton,* and *K. Folkers,* 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., M 23 (1967).

[21] *P. J. Rietz, F. S. Skelton,* and *K. Folkers,* Int. J. Vitamin Res. *37*, 405 (1967).

[22] *F. S. Skelton, K. D. Lunan, K. Folkers, J. V. Schnell, W. A. Siddiqui,* and *Q. M. Geiman,* Biochemistry *8*, 1284 (1969).

[23] *F. S. Skelton, P. J. Rietz,* and *K. Folkers,* J. Med. Chem. *13*, 602 (1970).

[24] *J. V. Schnell, W. A. Siddiqui, Q. M. Geiman, F. S. Skelton, K. D. Lunan,* and *K. Folkers,* J. Med. Chem. *14*, 1026 (1971).

[25] *K. Folkers,* Int. J. Vitamin Res. *39*, 337 (1969).

[26] *L. F. Fieser, J. P. Schirmer, S. Archer, R. R. Lorenz,* and *P. I. Pfaffenbach,* J. Med. Chem. *10*, 513 (1967).

[27] This information was kindly made available to us through the Walter Reed Army Institute of Research, Washington, D. C.

[28] *L. F. Fieser, M. Z. Nazer, S. Archer, D. A. Berberian,* and *R. G. Slighter,* J. Med. Chem. *10*, 517 (1967).

[29] *D. A. Berberian, R. G. Slighter,* and *H. W. Freele,* J. Parasitology *54*, 1181 (1968).

[30] *F. S. Skelton, R. S. Pardini, J. C. Heidker,* and *K. Folkers,* J. Amer. Chem. Soc. *90*, 5334 (1968).

[31] *L. Szarkowska,* Arch. Biochem. Biophys. *123*, 539 (1968).

[32] *F. L. Crane et al.,* personal communication.

[33] *R. E. Howells, W. Peters,* and *J. Fullard,* Ann. Trop. Med. Parasitol. *64*, 203 (1970).

[34] *C. D. Fitch,* Proc. Nat. Acad. Sci. *64*, 1181 (1969).

[35] *P. B. Macomber, R. L. O'Brien,* and *F. E. Hahn,* Science *152*, 1374 (1966).

[36] *R. Cadda* and *H. Sprinz,* Proc. Soc. Exp. Biol. Med. *130*, 524 (1969).

[37] *J. C. Catlin, R. S. Pardini, G. D. Daves, Jr., J. C. Heidker,* and *K. Folkers,* J. Amer. Chem. Soc. *90*, 3572 (1968).

[38] *J. C. Catlin, G. D. Daves, Jr.,* and *K. Folkers,* J. Med. Chem. *14*, 45 (1971).

[39] *R. S. Pardini, J. C. Catlin, J. C. Heidker*, and *K. Folkers*, J. Med. Chem. *15*, 195 (1972).

[40] *A. Castelli, E. Bertoli, G. P. Littarru, G. Lenaz*, and *K. Folkers*, Biochem. Biophys. Res. Commun. *42*, 801 (1971).

[41] *Y. T. Pratt* and *N. L. Drake*, J. Amer. Chem. Soc. *77*, 4664 (1955).

[42] *Y. T. Pratt* and *N. L. Drake*, J. Amer. Chem. Soc. *79*, 5024 (1957).

[43] *T. H. Porter, F. S. Skelton*, and *K. Folkers*, J. Med. Chem. *14*, 1029 (1971).

[44] *T. S. Osdene, P. B. Russell*, and *L. Rane*, J. Med. Chem. *10*, 431 (1967).

[45] *C. M. Bowman, F. S. Skelton, T. H. Porter*, and *K. Folkers*, J. Med. Chem. *16*, 206 (1973).

[46] *F. S. Skelton, C. M. Bowman, T. H. Porter*, and *K. Folkers*, Biochem. Biophys. Res. Commun. *43*, 102 (1971).

[47] *F. S. Skelton, T. H. Porter, G. P. Littarru*, and *K. Folkers*, Int. J. Vitamin Res. *43*, 150 (1973).

[48] *Y. T. Pratt* and *N. L. Drake*, J. Amer. Chem. Soc. *77*, 37 (1955).

[49] *C. E. Dalgleish*, J. Amer. Chem. Soc. *71*, 1697 (1949).

[50] Netherlands Patent Application 65-05, 524, Farbenfabriken Bayer A. G., Chem. Abstr. *64*, 11 215 h (1965).

[51] *T. H. Porter, F. S. Skelton*, and *K. Folkers*, J. Med. Chem. *15*, 34 (1972).

[52] *T. H. Porter, F. S. Skelton, C. M. Bowman*, and *K. Folkers*, J. Med. Chem. *15*, 504 (1972).

[53] *T. H. Porter, C. M. Bowman*, and *K. Folkers*, J. Med. Chem. *16*, 115 (1973).

[54] *Y. P. Wan, T. H. Porter*, and *K. Folkers*, Proc. Nat. Acad. Sci. USA *71*, 952 (1974).

[55] *L. Rane* and *D. S. Rane*, Proc. Helminth. Soc. Washington *39*, spec. issue, 283 (1972).

[56] *C. M. Bowman, R. J. Wikholm, J. Boler, C. B. Bogentoft*, and *K. Folkers*, J. Med. Chem. *16*, 988 (1973).

[57] *R. J. Wikholm, Y. Iwamoto, C. B. Bogentoft, T. H. Porter*, and *K. Folkers*, J. Med. Chem. *17*, 893 (1974).

[58] *T. H. Porter, A. von Klaudy*, and *K. Folkers*, J. Med. Chem. *16*, 1310 (1973).

[59] *M. D. Friedman, P. L. Stotter, T. H. Porter*, and *K. Folkers*, J. Med. Chem. *16*, 1314 (1973).

[60] *C. Bogentoft, A. von Klaudy*, and *K. Folkers*, J. Med. Chem. *15*, 1135 (1972).

[61] *E. F. Rogers, R. L. Clark, A. A. Pessolano, H. J. Becker, W. J. Leanza, L. H. Sarett, A. C. Cuckler, E. McManus, M. Garzillo, C. Malanga, W. H. Ott, A. M. Dickinson*, and *A. Van Ederstine*, J. Amer. Chem. Soc. *82*, 2974 (1960).

[62] *A. Goth*: Medical Pharmacology. C. V. Mosby Co., St. Louis 1961, p. 497.

Enzymatic Reduction of Ribonucleotides: Biosynthesis Pathway of Deoxyribonucleotides

By Hartmut Follmann[*]

Ribonucleotide reductases are enzymes that synthesize the deoxyribonucleotides required for the replication of DNA in dividing cells. They thus have a key function for the growth of microorganisms and of all plant and animal tissues. The enzymes reduce all four purine and pyrimidine ribonucleotides (as the 5'-diphosphates or triphosphates) with direct substitution of the 2'-hydroxyl group by hydrogen. The physiological reducing agents are the mercapto groups of thioredoxins, a group of small proteins, which are regenerated from the oxidized form by NADPH-dependent thioredoxin reductases. There are two known types of ribonucleotide reductases (I and II), which catalyze hydrogen transfer with the aid of protein-bound iron ions or of 5'-deoxyadenosylcobalamin (coenzyme B_{12}); free radicals can be detected in both cases. The enzymes are regulated by effector nucleotides. There may exist a homeostatic mechanism, which guarantees the supply of DNA precursors to the cell.

1. Deoxyribonucleotides as Building Units of DNA

In a bacterium or growing cell, before new deoxyribonucleic acid (DNA), the macromolecular carrier of the genetic information in the chromosomes, can be synthesized during cell division, its monomeric building units must be available in the cell as substrates of the replicating enzymes. This condition seems obvious, but among the numerous processes in the synthesis of nucleic acids[1] (Fig. 1), surprisingly little is known about the formation of the four deoxyribonucleotides (step b), in contrast with the very extensively studied biosynthesis of the purine and pyrimidine ribonucleotides (step a). Similarly, the polymerization of deoxyribonucleotides (step c) *in vivo* has not yet been fully elucidated in all important details. Though the 5'-triphosphates of deoxyadenosine, deoxycytidine, deoxyguanosine, and thymidine (dATP, dCTP, dGTP, and dTTP[**]) are generally considered the immediate precursors of DNA, an enzymatic polymerization of the corresponding 5'-diphosphates is also known[2], and a DNA replication at the level of 5'-monophosphates activated in some other way has been suggested[3].

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[**] The 5'-phosphates of the ribonucleosides adenosine (A), cytidine (C), guanosine (G), and uridine (U) and of the deoxyribonucleosides deoxyadenosine (dA), deoxycytidine (dC), deoxyguanosine (dG), and thymidine (dT) are denoted in the usual manner by the abbreviations –DP (diphosphate) and –TP (triphosphate); (d)N is an unspecified (deoxy)ribonucleoside. DNA: deoxyribonucleic acid, RNA: ribonucleic acid, FAD: flavin adenine dinucleotide, NADPH and NADP: reduced and oxidized nicotinamide adenine dinucleotide phosphate respectively. For the structures of these compounds cf. *W. Saenger*, Angew. Chem. *85*, 680 (1973); Angew. Chem. internat. Edit. *12*, 591 (1973).

All these deoxyribonucleotides are present in the cell only in minute steady-state concentrations. They can hardly be detected by direct analysis in the presence of the chemically similar ribonucleotides, whose concentrations are higher by

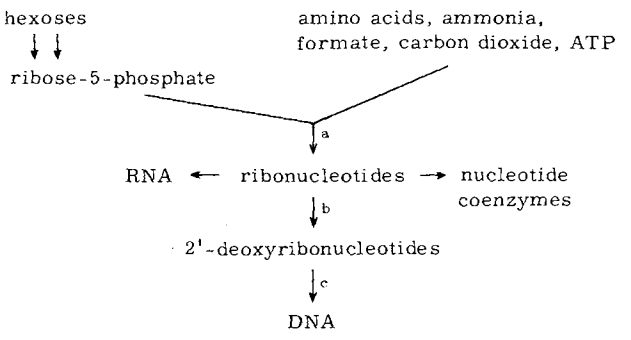


Fig. 1. Dependence of the DNA replication (step c) on the purine and pyrimidine biosynthesis (step a) and the ribonucleotide reduction (step b) in the course of the *de-novo* nucleic acid biosynthesis.

a factor of 10 to 100. It is only recently[4,5] that the deoxyribonucleoside triphosphates present in a tissue extract can be quantitatively determined in amounts of less than 1 pmole with the aid of DNA polymerase I and synthetic polynucleotide templates *in vitro*. Pools of the order of 10–100 pmole of dNTP per 10^6 cells were found in cell cultures of mice[6,7] and of hamsters[8,9] and in ascites tumor cells[10], these quantities being distributed between the cell nucleus and the cytoplasm[11]. They exhibit considerable growth-dependent variations[9,108], but they can only sustain DNA replication for about 1—5 min in any case. Only oocytes such as those of the frog *Xenopus laevis* appear to be better supplied with DNA precursors, since the pool of 12 pmole of dNTP per cell found here[12] is sufficient for the synthesis of the DNA of more than 2000 new cell nuclei.

There are two possible routes for replenishment of the deoxyribonucleotide pools, *i.e.* reutilization of DNA fragments such as thymidine from the catabolic metabolism or supplied from outside, or complete synthesis of new material[13]. The first route ("salvage pathway") is essential for auxotrophic microorganisms; it requires a series of inducible enzymes such as nucleoside deoxyribosyl transferases, nucleoside phosphorylases, and nucleoside kinases, which can separate the bases, sugars, and phosphate residues of the nucleotides from one another and recombine them.

Since all other organisms synthesize DNA without the supply of deoxyribonucleotides and make practically no use of nutritive nucleic acids, they must all be capable of *de-novo* synthesis. The pentose component of the nucleic acids is obtained here from the oxidative and non-oxidative carbohydrate metabolism of the cell, as can be shown *e.g.* by the isotope content of the RNA and DNA when *Escherichia coli* is cultured on ^{18}O-labeled glucose or fructose[14]. In none of these pathways is free 2-deoxyribose formed and then incorporated into nucleotides; the enzyme deoxyribose aldolase that is in principle able to synthesize this sugar from glyceraldehyde-3-phosphate and acetaldehyde[15] probably catalyzes only the degradation of 2-deoxyribose-5-phosphate *in vivo*[16]. The biosynthesis of all nucleotides proceeds instead from ribose-5-phosphate, with construction of the heterocyclic bases (Fig. 1) to form ribonucleotides, from which the deoxyribonucleotides are formed in a further reaction, with retention of the *N*-glycoside linkage between the sugar and the base. This relationship was first demonstrated by *Reichard* in 1950 in the utilization of ^{15}N-labeled cytidine (but not cytosine) for RNA *and* DNA in the metabolism of the living rat[17]. The conversion of ^{14}C-labeled ribonucleosides into deoxyribonucleotides was also detected first in microorganism cultures[18] and later in cell-free extracts (*e.g.* from *E. coli*[19]).

Enzymes that reduce ribonucleoside-5'-phosphates with replacement of the 2'-hydroxyl group by hydrogen to form 2'-deoxyribonucleotides are known as ribonucleotide reductases[20]. The reducing agents in every known case are dithiols, which are converted into the disulfide and regenerated in a further enzyme reaction. There are only few reviews of these reactions[1,13,21,22]. The present report deals with our current knowledge of the occurrence and the structure of ribonucleotide reductases, their reaction mechanism, and their unusual regulation phenomena. Numerous investigations during the past few years have shown that these enzymes, to which little attention had previously been given, are of outstanding importance to the development of all life forms.

2. Ribonucleotide Reductases

2.1. Occurrence, Isolation, and Detection

Ribonucleotide reductases, as inducible enzymes very closely connected with cell proliferation, are most easily found in rapidly growing cell cultures and tissues; great difficulty is encountered in their detection in resting tissues. Bacteriophages, microorganisms in the exponential growth phase, germinating plant seeds, embryonic or regenerating animal organs and tumors are typical materials for the isolation of ribonucleotide reductases (Table 1). The majority of the known enzymes come from bacteria and mammalian tissues, whereas the reduction of ribonucleotides in plants, for example, has not yet been very extensively studied. The reductases of *Escherichia coli*, of *Lactobacillus leichmannii*, and from Novikoff tumors, which have been under investigation for some time by the research groups of *Reichard* (Stockholm), *Blakley* (Iowa City), and *Moore* (Houston), exhibit a number of properties that are typical of all enzymes, but the deoxyribonucleotide synthesis as a whole exhibits many species-specific peculiarities in most organisms.

The very limited knowledge of the reduction of ribonucleotides that existed until recently bears witness to the difficulties of dealing with these enzymes. They always occur in small quantities and are often unstable proteins, so that they are not easy to purify by conventional methods (*e.g.* from yeast[32] or wheat[33]). A successful use of affinity chromatography with insolubilized coenzyme B_{12}[51] or dATP[52] for the purification of the ribonucleotide reductases from *L. leichmannii*, *E. coli*, and the bacteriophage T4 promises progress in this respect.

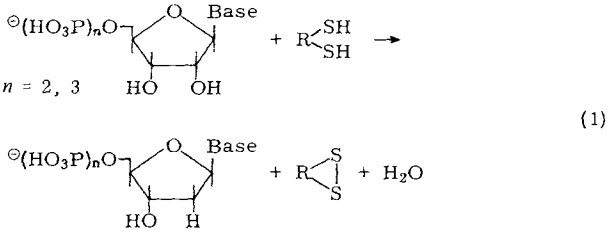
Ribonucleotide reductases are also much more difficult to determine quantitatively than most other enzymes. There is no fast routine assay for the simple reaction (1) that is catalyzed by them. The most common method makes use of a radioactive substrate such as [5-^3H]CDP, the resulting labeled deoxyribonucleotide being determined after separation by paper, column[53,118], or thin layer chromatography[54]; this test is

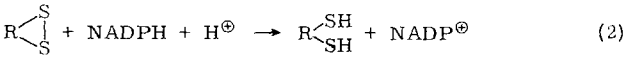
Table 1. Ribonucleotide reductase activity in extracts of various organisms and tissues.

Source	Type [a]	Substrates	Cofactors	Ref.
Prokaryotes				
Escherichia coli	I	NDP	Fe, ATP, Mg	[19]
Bacteriophage T4 on *E. coli*	I	NDP	Fe, ATP, (Mg)	[23, 24]
Lactobacillus leichmannii	II	NTP	coenzyme B_{12}	[25]
Clostridium sticklandii	II		coenzyme B_{12}	[26]
Rhizobium meliloti	II	NDP, NTP	coenzyme B_{12}	[27]
Corynebacterium nephridii	II	NDP	coenzyme B_{12}	[28]
Pseudomonas stutzeri	II		coenzyme B_{12}	[28]
Micrococcus denitrificans	II		coenzyme B_{12}	[28]
Bacillus megaterium	II		coenzyme B_{12}	[29]
Thermus X-1 (aquaticus)	II	NTP	coenzyme B_{12}	[30, 28]
Eukaryotes				
Euglena gracilis, Astasia longa (algae)	II	NTP	coenzyme B_{12}	[28, 31]
Saccharomyces cerevisiae (yeast)	I	NDP	Mg, ATP	[32]
Wheat germ	I	NDP	Fe, ATP	[33]
Soy bean, broad bean	I	NDP		[34]
Sea urchin eggs (*Arbacia punctulata*)	I	NDP	Mg, ATP	[35]
Silkmoth (*Hyalophora cecropia*)	I			[36]
Chick embryo	I			[37]
Rat embryo	I	NDP		[38]
Thymus (calf)	I			[39, 68]
Kidney (mouse)	I			[40]
L cells (mouse)				[41]
Regenerating liver (rat)	I	NDP	Fe, ATP, Mg	[42, 43]
Bone marrow in case of pernicious anemia (man)				[44]
Bone marrow in case of reticulocytosis (rabbit)	I	NDP	Fe, ATP, Mg	[45]
Spleen (leukemic mouse)	I	NDP	Mg	[46]
Embryonic brain (chick, rat, man)	I	NDP	Mg	[47]
Ehrlich ascites cells	I	NDP		[39, 118]
Novikoff ascites tumor (rat)	I	NDP	Fe, ATP, Mg	[48]
Yaba tumor virus (rhesus monkey)	I	NDP		[49]
Walker, Morris and other rat tumors	I	NDP		[50]

[a] See Sections 2.2.1 and 2.2.2.

subject to interference by other nucleotide-transforming enzymes, particularly in crude extracts. A less sensitive method is the colorimetric determination of deoxyribose with diphenylamine; in this case, the deoxyribonucleotide formed must





first be hydrolyzed with acid[55]. A method that is also suitable for kinetic measurements simulates the physiological process, the reaction (1) being coupled with the regeneration of the dithiol thioredoxin by thioredoxin reductase [reaction (2)], and the NADPH consumption being followed spectrometrically[56]; however, purified enzymes and thioredoxin of suitable specificity are necessary for this enzyme determination. Finally, the coenzyme B_{12}-dependent ribonucleotide reductases (enzymes of type II in Table 1) can be determined by the liberation of tritium from [5′-^{3}H]-5′-deoxyadenosylcobalamin (coenzyme B_{12}, see below) during the reduction. The radioactive water formed is sublimed out of the reaction solution for this determination[26, 57].

2.2. Specificity of the Enzymes

All purified ribonucleotide reductases catalyze the reduction of the four natural ribonucleotides (and also of ribonucleotides with non-natural bases) by the same enzyme protein; there is no indication that the other systems contain several enzymes that are specific for individual nucleotides. All the ribonucleotide reductases are also alike in that they accept low molecular weight dithiols such as dithioerythritol or reduced lipoic acid as reducing agents *in vitro*, and they require the 5′-diphosphates or 5′-triphosphates of the ribonucleosides as substrates. Reduction at the 5′-monophosphate level does not seem to occur, though nucleotide kinases may give the incorrect impression that it does occur in unpurified extracts. However, the ribonucleotide reductases must be divided into two very different groups according to cofactor requirement and protein nature.

2.2.1. Ribonucleoside Diphosphate Reductases (EC 1.17.4.1)

Enzymes of type I (Table 1), represented by that from *E. coli*, are found in microorganisms, plants, and animals as high as man. So far as is known, they always reduce the diphosphates ADP, CDP, GDP, and UDP. A characteristic of this group is that instead of catalyzing the redox reaction (hydrogen transfer) between dithiol and ribose with the aid of one of the conventional coenzymes, they contain protein-bound iron ions, which are essential for the activity of the enzyme. The existence of such an enzyme is therefore often recognized by the fact that reduction of ribonucleotides is

stimulated by low concentrations of iron salts or inhibited by complexing agents for iron. The enzyme reaction is inhibited particulary specifically by hydroxyurea[58] and by 1-formylisoquinoline thiosemicarbazone[59]; however, this inhibition is only partly reversible, and probably also leads to further changes in the proteins. Many of these enzymes also require magnesium ions and ATP (as an effector, and not as an energy source) for their activity. It is not yet possible to say whether this is true of all reductases of type I.

2.2.2. Ribonucleoside Triphosphate Reductases (EC 1.17.4.2)

Type II (Table 1) comprises enzymes whose hydrogen transfer reaction involves 5'-deoxyadenosylcobalamin. This coenzyme form of vitamin B_{12} catalyzes several enzymatic hydrogen shifts *via* the 5'-methylene group of its adenosyl residue (cf. Fig. 3)[60]; its participation in the reduction of ribonucleotides was first detected by *Blakley* and *Barker*[25] in a cell-free extract of *Lactobacillus*. A number of enzymes can evidently also use diphosphates as substrates instead of the triphosphates ATP, CTP, GTP, and UTP. They are not greatly affected by metal ions. Apart from the lower algae *Euglena*, the coenzyme B_{12}-dependent ribonucleotide reductases seem to occur only in prokaryotes (organisms without cell nuclei). Their distribution in many microorganisms has been investigated by the very sensitive test with radioactive coenzyme[28], but there is no regularity of occurrence here, even in closely related species. Many attempts have been made to demonstrate the participation of B_{12}-dependent reductases in the DNA synthesis of mammals, particularly in the unbalanced DNA formation in the megaloblasts of the bone marrow in pernicious anemia, but the action of vitamin B_{12} in these systems is definitely not connected with the reduction of ribonucleotides[44].

2.3. Protein Structure

Only a few of the ribonucleotide reductases listed in Table 1 have been purified sufficiently for detailed analyses of their protein structure and of the bonding of substrates and effectors. No far-reaching comparisons are possible from a glance at Table 2. Nevertheless, it can be seen that several iron-dependent reductases are large proteins with two dissimilar components, each of which is inactive by itself, and which may be regarded as a regulatory subunit and a catalytic subunit. Thus in the case of the separated pure subunits of the enzyme from *E. coli*[61], protein B1 has at least four different kinds of nucleotide binding sites[65], whereas B2 binds two iron atoms, but no nucleotides. Their enzymatically active 1:1 complex is formed in the presence of magnesium ions and the positive effector dTTP; binding of the inhibitor dATP leads to an inactive, aggregated protein. The amino acid analysis and other properties of this enzyme system have been reported[66].

The manner in which the iron atoms are bound is particularly interesting in these proteins. In the *E. coli* protein B2, they are inert to reducing and oxidizing agents and are not bonded to inorganic sulfur (as in other "non-heme iron" compounds); they can be removed from the protein by careful dialysis against 8-hydroxyquinoline 5-sulfonate and imidazole, and can be reconstituted to give a fully functional B2 by treatment of the enzymatically inactive apoprotein with iron(II) ascorbate[67].

The UV absorption spectrum of the metalloprotein, like the Mössbauer spectrum (recorded for the [^{57}Fe]protein B2)[67], points to a close structural relationship with the hemerythrins; in these oxygen-transporting proteins of marine worms and brachiopods, there are two "high-spin" iron(III) ions in an antiferromagnetically coupled (*i. e.* as a whole diamagnetic) binuclear complex, whose protein ligands are unknown. The function of the iron in B2 is evidently not the transport of either oxygen or electrons; it serves for the production and stabilization of an organic radical that is also detectable in the subunit B2 and that is probably involved in the reduction (see Section 3.1.). The T4 phage enzyme[62] is very similar in all these properties to the enzyme from *E. coli*.

The coenzyme B_{12}-dependent reductases seem to have somewhat simpler structures. The relatively small *Lactobacillus* enzyme combines all the catalytic and regulatory binding sites (at least four for the substrate, coenzyme, and effectors) in a single polypeptide chain, which is not unusually long[64]. Its amino acid analysis and initial attempts to prepare large protein fragments have been described; kinetic and mechanistic studies are particularly well advanced for this enzyme.

Table 2. Protein structure of purified ribonucleotide reductases.

Source and purity	M.wt. and/or sedimentation coefficient	Properties	Ref.
Escherichia coli (homogeneous)	245000 9.7–10.1 S	Separable by chromatography into B 1 (m.wt. 160000, 2 peptide chains) and B 2 (m.wt. 78000, 2 peptide chains); B 1 binds nucleotides, B 2 contains 2 atoms of Fe (light abs. 360, 410 nm); B 1 : B 2 complex stabilized by Mg; in presence of dATP inactive dimer	[61]
Phage T4 (homogeneous)	225000	1 Protein having 2 atoms of Fe (light abs. 360, 410 nm), only slightly stabilized by Mg; denaturing electrophoresis yields 2 pairs of peptide chains having m.wt. 80000 and 35000 resp.	[62]
Rat liver (300×)	6.6 S	Aggregated and inactivated in presence of dATP	[42]
Bone marrow (50×)		Separable by chromatography into 2 dissimilar proteins S 1 and S 2, inactive when separated	[45]
Novikoff tumor (150×)		2 Dissimilar proteins P1 and P2	[63]
L. leichmannii (homogeneous)	76000	1 Polypeptide chain (*ca.* 690 amino acids), incapable of dissociation or aggregation	[64]
Thermus X-1	80000	Activity maximum at 70 °C, stable up to 80 °C; effector action only at elevated temperature (change of conformation?)	[30]

2.4. Subcellular Localization

The localization of the ribonucleotide reductases in the cell has not yet been systematically studied. They are generally thought to be cytoplasmic enzymes, since little or no reductase activity is found in cell nuclei, mitochondria, and microsomes of rat liver[42] or of Novikoff tumors[68]. There have recently been indications that these tissues contain ribonucleotide reductase as an enzyme complex together with other enzymes of the DNA biosynthesis, *i. e.* thymidylate synthetase, thymidylate kinase, and DNA polymerase II[68,69]. These enzyme activities sedimented in the ultracentrifuge with a postmicrosomal membrane fraction of unknown origin, and after breakdown of the membrane fragments they were visible in the electron microscope as particles with a size of 8.5—12 nm. The membrane component does not seem to be essential to the activity and cohesion of the enzymes. Similar material with a high reductase activity has also been isolated from thymus, spleen, and HeLa cells.

body temperature? Deoxygenations at high temperatures or catalytic hydrogenations can hardly be cited as non-enzymatic parallels for nucleotide molecules, and the only known chemical conversion of a ribonucleotide (AMP) into the corresponding deoxyribonucleotide by linkage of the 2'-hydroxyl group and the adenine base followed by removal of sulfur from the intermediate 8,2'-anhydroadenosine thioether [reaction (3)][70] also does not proceed under physiological conditions.

The high specificity of the enzyme reaction for ribonucleotides with an intact 2',3'-*cis*-diol grouping[81] can be interpreted by multiple fixation of the substrates to the protein *via* the phosphate ions, the purine or pyrimidine base, and the 3'-hydroxyl group (cf. Fig. 4), but an explanation of the redox reaction itself presents both chemists and enzymologists with a problem that is as difficult as it is interesting.

The fate of the atoms and groups involved has been so thoroughly studied in the enzymes from *E. coli* and *L. leichmannii* with isotope-substituted model nucleotides and spectroscopic techniques that, despite the very different protein structures

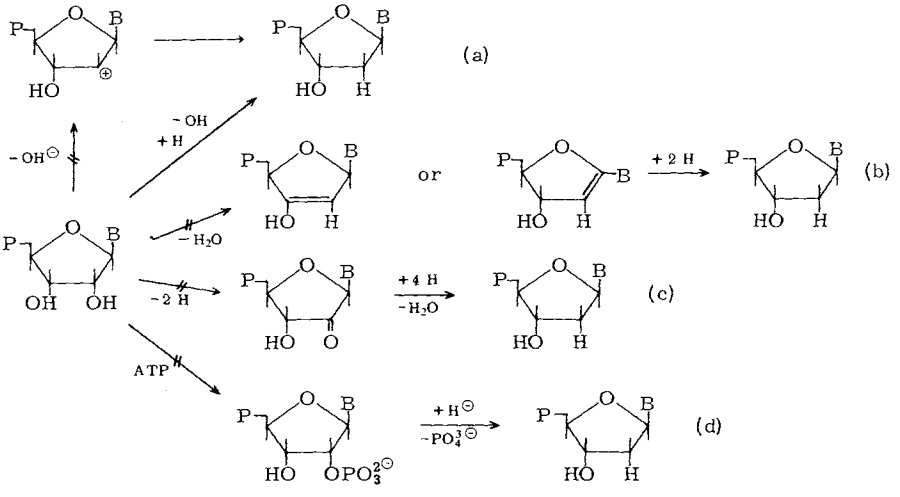
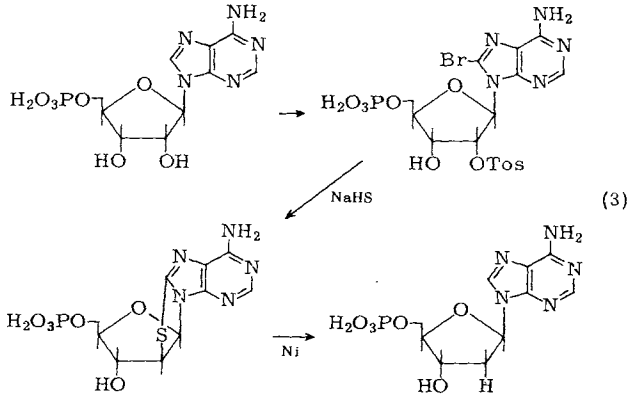


Fig. 2. Possible reaction pathways for the replacement of the 2'-hydroxyl group of ribose by hydrogen: a) direct substitution, b) dehydration-hydrogenation, c) oxidation-reduction, d) activation by ATP. P = phosphate residue, B = purine or pyrimidine base.

3. Mode of Action and Regulation

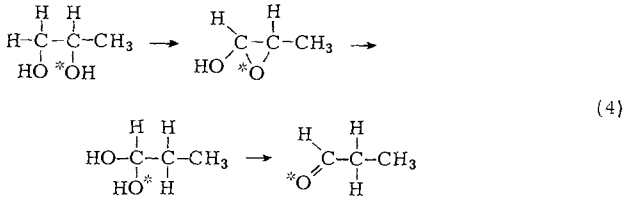
3.1. Reduction of the Hydroxyl Group

How is one of the two secondary hydroxyl groups of ribose selectively reduced to a methylene group at pH = 7 and at



and cofactors, it is conceivable that the modes of action of these two bacterial reductases are fundamentally similar. It may be taken as certain that the 2'-hydroxyl group is reduced directly without the existence of intermediate products [Fig. 2(a)]. The experiments mentioned below rule out reaction sequences such as dehydration-hydrogenation (b) or oxidation-reduction (c), and activation of the hydroxyl group by phosphorylation (d) likewise cannot be detected, since synthetic cytidine-2'-phosphate-5'-diphosphate is not a reductase substrate[71]. In both systems, only one new hydrogen atom enters the molecule with retention of configuration at the asymmetric $C^{2'}$. This follows from chemical[72,73] and NMR-spectroscopic analyses[74,75] of the monodeuterated (or monotritiated) 2'-deoxyribonucleotides obtained when the enzymatic reduction is carried out in ^2H_2O or ^3H_2O and hence with deuterated or tritiated dithiols $R(S^*H)_2$ as the reducing agent. The assignment of the enzymatically formed products has also been confirmed by independent synthesis of the two epimeric [2'-(α- or β-)deutero]-2'-deoxycytidines[76]. These results are compatible only with the direct pathway (a), and at the same time refute an S_N2 substitution of the hydroxyl group with inversion, which is improbable in any case at the furanose ring.

The coenzyme B_{12}-dependent enzyme diol dehydrase from *Aerobacter aerogenes* catalyzes an oxidoreduction of propanediol to propionaldehyde, which seems to be related to the reduction of ribonucleotides, and which proceeds with migration of oxygen *via* an epoxide intermediate [reaction (4)][77]. By reaction of specifically ^{18}O-labeled adenosine triphosphates[78] with *Lactobacillus* ribonucleotide reductase, we have



(4)

shown that no intramolecular migration of the oxygen atoms 2′ and 3′ occurs in this system; $O^{2'}$ disappears completely from the molecule, and $O^{3'}$ in [3′-^{18}O]ATP is not affected by the reduction. However, if [2′-^{18}O]ATP is incubated with enzyme and coenzyme in the absence of reducing agent, no equilibration of the isotope content of $O^{2'}$ with $H_2{}^{16}O$ occurs, *i.e.* a conventional S_N1 reaction with ionization at $C^{2'}$ also does not take place by route (a)[79]. The isotope pattern of the RNA and DNA from *E. coli* in a medium containing ^{18}O, which is identical apart from $O^{2'}$[14], shows that here again the 2′-oxygen is eliminated by reduction in the same direct way.

Nucleotides in which the free 2′-OH group is replaced by a phosphate residue[71], by a methoxy[81], amino, azido, or chloro substituent[80], or by an OH group in the *arabino* configuration[81] are not transformed by ribonucleotide reductase; however, 3′-*xylo*nucleotides, 3′-deoxyribonucleotides[82,83] and 3′-*O*-methylribonucleotides are also not reduced[81]. Since most of these compounds are not effective inhibitors, we assume that the 3′-hydroxyl group is a binding site for the enzyme, and that substrate *binding* (on 3′-OH) and substrate *reduction* (on 2′-OH) are concerted. All these findings can be formally compared to an S_Ni reaction, in which the exchange of the hydroxyl group takes place in a prefixed complex with several reaction partners (enzyme groups and reducing agent) with retention of configuration.

There is much less clarity about the hydrogen transfer between thioredoxin or another dithiol and the 2′-position of ribose. There is growing experimental evidence that free-radical intermediates, which are stabilized by the cofactors (iron atoms in *E. coli*, 5′-deoxyadenosylcobalamin in *L. leichmannii*), occur in this process. Thus an organic free radical that is characterized by a light absorption at 410 nm and an ESR signal at $g = 2.0047$, and whose destruction (*e.g.* by hydroxylamine) is exactly paralleled by a loss of the enzyme activity, is observed in the metalloprotein B2[67]. A hydrogen-transferring function of the coenzyme in the *Lactobacillus* reductase system can be detected even more directly. It has been known for some time that this enzyme, in the presence of dithiols and an effector such as dGTP, catalyzes a tritium exchange between synthetic [5′-^{3}H]-5′-deoxyadenosylcobalamin and water (which is used as an activity test) or conversely between ^3H_2O and unlabeled coenzyme, and that this tritium exchange and the substrate reduction are inhibited to the same extent by protein reagents such as *N*-bromosuccinimide[26,57]. The reactive intermediate, in which there must be *three* equivalent hydrogen atoms on $C^{5'}$ of the coenzyme, was recently discovered by fast-reaction techniques[84,85]; with a half-life in the region of 10—100 ms, one observes a change from the spectrum of the coenzyme (with trivalent cobalt as a central atom) to a spectrum of reduced cob(II)alamin and the appearance of an ESR signal at $g = 2.119$, which can be reconciled with an enzyme-fixed complex of the free radicals [$>Co^{2+}<$] and [5′-deoxyadenosyl·]. The concentration of this intermediate rapidly decreases again in the presence of substrate. 5′-Deoxyadenosine and aquocob(II)alamin are also formed in a slow, irreversible reaction, with the appearance of other ESR signals[86]. It may be assumed that the deoxyadenosyl radical formed by reversible homolysis of the Co—C bond in the coenzyme is responsible, in conjunction with one or more thiol groups, both for the hydrogen exchange and for the reduction of the ribose (Fig. 3).

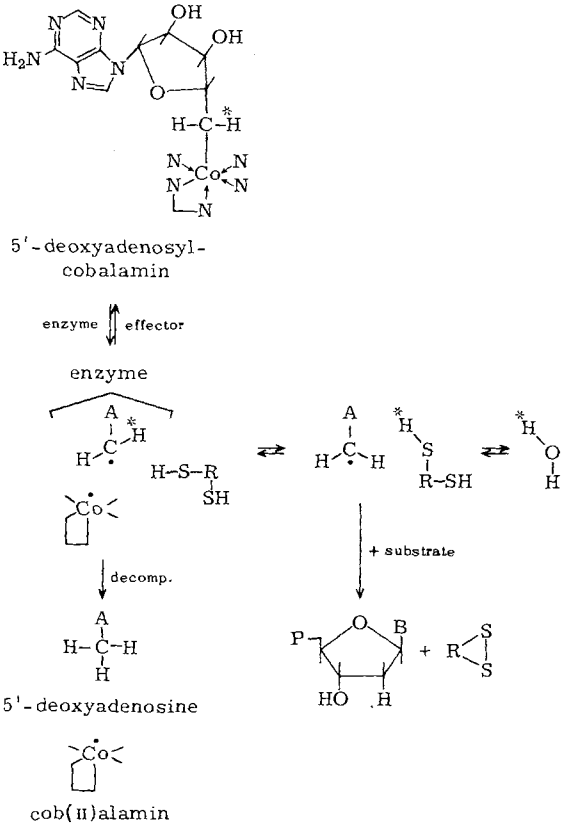


Fig. 3. Structure and function of 5′-deoxyadenosylcobalamin (coenzyme B_{12}) in the ribonucleotide reductase from *L. leichmannii* (modified after [84]). The transfer of a hydrogen isotope (*) from labeled coenzyme to water or from water to the coenzyme or the substrate is shown. A = adenosine – $C^{5'}$, B = purine or pyrimidine base, P = phosphate residues, R = thioredoxin or dithiol. The corrin ring system and the lower axial ligand of the cobalt are only indicated.

A separate analysis of the nature of the hydrogen transfer as the final step of the reduction of substrate in such enzyme-radical-thiol complexes will prove very difficult. No ESR signal that could be assigned to a nucleotide radical has been observed so far. It is therefore impossible at present to say

whether the hydroxyl group is finally replaced by a hydrogen atom or by a hydride ion. An answer to this question would also require a precise knowledge of the amino acid side chains in the catalytic center of the proteins, since the hydroxyl group could, *e.g.*, be specifically protonated by these side chains and removed as a water molecule. (So far it has only been shown that cysteine residues are probably involved in the activity of both bacterial reductases[66, 87].) From all the observations taken together, one may expect a highly ordered transition state from the substrate, amino acid groups of the enzyme, and a reduced species from cofactors and SH groups; Figure 4 is an attempt to describe this transition state in the form of a "snapshot".

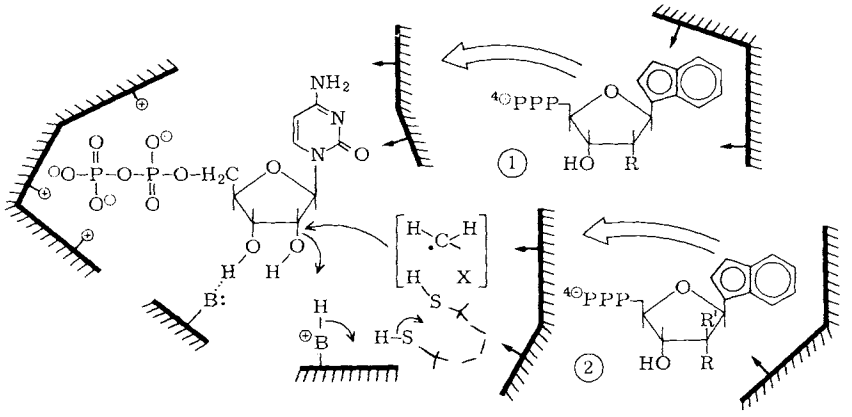


Fig. 4. Hypothetical model of the active site of a ribonucleotide reductase. The substrate (cytidine diphosphate) is fixed to the protein *via* the terminal phosphate residues and the 3'-hydroxyl group; the quality of the bonding to the purine or pyrimidine base depends on an allosteric effector ①. The reduction of $C^{2'}$ is stimulated by other effectors ②, which optimize the bonding of the hydrogen-donating system. X is the iron complex or cob(II)alamin radical of the type I and type II reductases respectively. Arro on the protein symbolize interactions of unknown nature. B = basic ami acid residue, P = phosphate, R,R' = H or OH.

In reality, however, the dynamic situation is even more complicated by the bonding of allosteric effectors to the enzyme.

3.2. Regulation of Enzyme Activity

Regulation of substrate reduction by effectors or modifiers is so characteristic of ribonucleotide reductases that its description would fill many pages[30, 57, 62, 65, 81–83, 88–91]. Primarily, deoxyribonucleoside triphosphates and ATP, and also modified nucleotides[81–83], accelerate or inhibit the catalysis by the enzyme, both the K_m values and the rate constants of the substrates being altered. Table 3 shows that there are similarities in this respect among the type I enzymes, but there are also great species-specific differences. A different picture is found for the regulation pattern in the case of the *Lactobacillus* reductase (Table 4), where in addition to slight product inhibition, a pronounced specific stimulation of the reduction of ATP by dGTP, of CTP by dATP, and of UTP by dCTP is observed[89]; even totally non-natural and slow-reacting nucleotides such such as (*N*-ribofuranosylbenzimidazole)-5'-triphosphate are subject to the stimulation[81].

Little is known about the detailed mode of action of the effectors, as in most cases of this type. A number of observations point to changes in the conformation of the protein, as is required by the model of an allosteric regulation[30, 42, 65, 66]. It is conceivable that the catalytic site of a reductase is thereby particularly well or less well ordered (Fig. 4). Extensive binding studies[21, 65] show that there are two classes of regulatory sites on the *E. coli* subunits, one of which controls the substrate specificity and the other the total activity of the enzyme.

Table 3. Effect of nucleoside triphosphates on the reduction of ribonucleotides: stimulation (+) and inhibition (−).

Effector	*E. coli* [65, 90]				T4 phage [62]				Novikoff tumor [88]			
	UDP	CDP	GDP	ADP	UDP	CDP	GDP	ADP	UDP	CDP	GDP	ADP
dTTP	+	+	+	+	+	+	+	+	−	−	+	+
dCTP					+	+						
dGTP			+	+			+	+	−	−	−	+
dATP	−	−	−	−	+	+	−		−	−	−	−
ATP	+	+			+	+			+	+	+	

Table 4. Relative reaction rates of the reduction of ribonucleotides by *Lactobacillus* reductase [81, 89].

Effector	GTP	ATP	UTP	CTP	ITP [a]	BzTP [b]
none	100	20	14	36	6	0.2
dGTP	86	103				2
dCTP			37	31		
dATP		15		102		
dTTP					38	
araATP		11		36		

[a] Inosine triphosphate.
[b] (*N*-Ribofuranosylbenzimidazole)-5'-triphosphate.

The *Lactobacillus* reductase also reacts to two groups of effector nucleotides, one of which again affects the substrate specificity and the other the enzyme-coenzyme interaction, including the tritium exchange[81]. A regulatory effect of the coenzyme concentration on the binding of substrate and effectors is also observed[89]. From the marked base specificity of all these effects, considerable binding contributions by the amino and keto substituents of the purine and pyrimidine bases can be expected in the catalytic and regulatory centers; these interactions have not yet been analyzed.

From the regulation phenomena listed in Tables 3 and 4, it seems natural to construct a homeostatic mechanism that guarantees a balanced supply of all four deoxyribonucleotides to the cell. If one nucleotide accumulates during DNA synthesis, it stimulates production of the others; on the other hand, if no further DNA is being formed, an accumulation of certain nucleotides inhibits further reduction of ribonucleotides. Detailed models of this kind have been devised[88-91]. The extent to which this regulation is actually achieved *in vivo* is admittedly difficult to estimate from the behavior of the isolated ribonucleotide reductases at partly unphysiological concentrations. Further unknowns are the rate and control of the biosynthetic pathways by which effector nucleotides (particularly dTTP) must first be formed from the primary reduction products (*e.g.* dUDP) before they can exert a feedback control[13]. However, changes in the deoxyribonucleotide pools in tissue cultures under the influence of thymidine and other nucleosides in the medium point to a functioning of allosteric regulation in intact cells[117].

4. The Hydrogen-Donating Thioredoxin System

The hydrogen required for the reduction of ribonucleotides ultimately comes from the cellular NADPH pool that is available for synthetic purposes, but it is used only through the intervention of a specific "redoxin". As was mentioned earlier (Section 2.1), the thioredoxin system, which was first discovered in *E. coli*, consists of the small protein thioredoxin, whose cysteine residues change reversibly between the dithiol and disulfide forms, and the flavoenzyme thioredoxin reductase, which is responsible for the reduction of the oxidized thioredoxin. If one includes the (probable) processes on enzymes and coenzymes, one thus obtains a multi-stage hydrogen and electron transport from NADPH to ribose (Fig. 5).

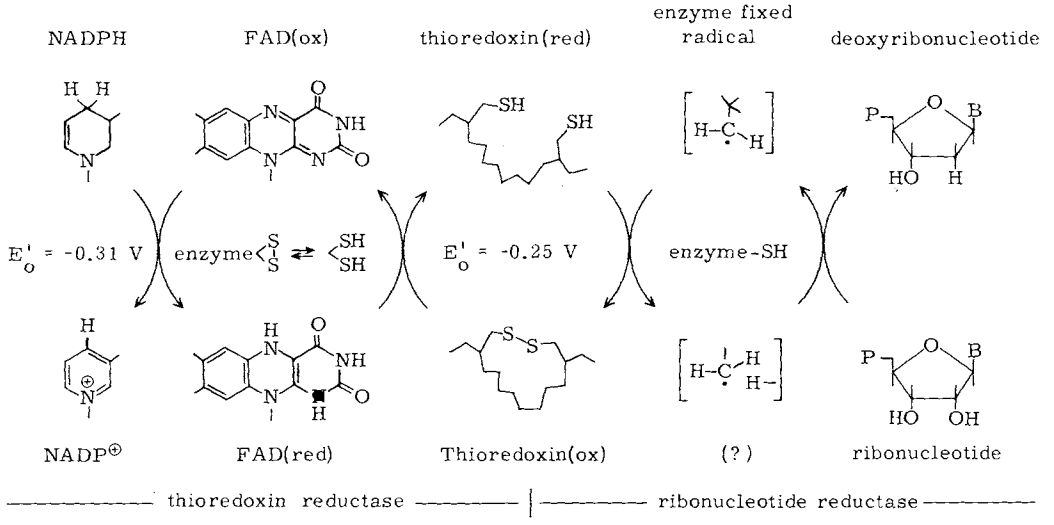


Fig. 5. Intermediate steps of the hydrogen transfer from NADPH to ribonucleotides by thioredoxin reductase and ribonucleotide reductase. In the penultimate stage, the structure of the 5'-deoxyadenosyl residue (type II reductases) is indicated (cf. Fig. 3). P = phosphate residues, B = purine or pyrimidine base.

Thioredoxins are heat-stable polypeptides built up from about 100 amino acids and having a molecular weight of about 12000, which have been isolated from the phage T4, from bacteria, from yeast, and from liver (Table 5). They themselves have no enzyme activity, but as an active site they contain two cysteine residues separated by two other amino acids: the sequence of this region in *E. coli* and yeast[101,102], is -Trp-Cys-Gly-Pro-Cys-Lys-, while the sequence in the T4 phage is -Lys-Cys-Val-Tyr-Cys-Asp-[93]. Oxidation to the disulfide with formation of a 14-membered ring is accompanied by considerable local changes in conformation, which are directly reflected in the changing tryptophan fluorescence of the molecules[103]. Like glutathione reductase, the NADPH-specific thioredoxin reductases, whose existence has also been detected in several tissues (Table 5), contain FAD as the

Table 5. Molecular weights and other properties of thioredoxin and thioredoxin reductases.

Source	Thioredoxin	Thioredoxin reductase	Ref.
Escherichia coli	11657, 108 amino acids, 2 Cys	66000–73000, 2 peptide chains, 2 FAD	[92, 99, 101, 104]
T4 phage	87 amino acids, 2 Cys	not detected	[93]
Lactobacillus leichmannii	12000	55000	[94]
Yeast	12600, *ca.* 120 amino acids, 4 Cys	75000, 2 subunits, 2 FAD	[95, 102, 119]
Rat liver	not yet purified to homogeneity		[96, 100]
Calf liver	12000, 103 amino acids, 4 Cys		[97]
Novikoff tumor	12100, 109 amino acids, 6 Cys	66700	[98]

prosthetic group; a disulfide grouping with the sequence -Ala-Cys-Ala-Thr-Cys-Asp- also takes part in the redox process in the *E. coli* enzyme[104].

Thioredoxins, thioredoxin reductases, and ribonucleotide reductases of different species have varying activities in heterologous mixtures, and no systematic pattern of interchangeability has been recognized so far. The readily obtainable *E. coli* thioredoxin has proved suitable as a hydrogen donor for the *Lactobacillus* and yeast ribonucleotide reductases[105,32], but is inactive toward the reductases of the T4 phage and of wheat[62,33]. Whereas the *E. coli* ribonucleotide reductase accepts all known thioredoxins, the thioredoxin reductase of the same bacterium is strictly specific for its own oxidized thioredoxin and that of T4 phage[93-95,98].

Reductions of ribonucleotides and of thioredoxin show practically no connection with other metabolic pathways in the cell. Only the participation of the thioredoxin system in the reduction of methionine sulfoxide and of sulfate in yeast has been detected[106], and the nitrate reduction and the ribonucleotide reduction in anaerobic microorganisms could have a common hydrogen-donor system[28]. The ribonucleotide reduction, in accordance with Figure 5, is not reversible; from what was said earlier, a general biosynthesis pathway from deoxyribonucleotides to ribonucleotides is not to be expected. However, an enzymatic hydroxylation of thymidine or 2'-deoxyuridine to ribothymidine or uridine occurs as the first step in the oxidative conversion of thymidine into uracil[107]. A pyrimidine-2'-deoxyribonucleoside 2'-hydroxylase isolated from the mold *Neurospora crassa* catalyzes this reaction with oxygen, ketoglutarate, iron(II) ions, and ascorbate as substrates and cofactors.

5. Ribonucleotide Reduction and Growth

Ribonucleotide reductase cannot be detected in dry wheat grains or in unfertilized sea urchin eggs, but within a few hours after the start of germination or after fertilization, extracts of these tissues exhibit the ability to reduce ribonucleotides[33,35]. If part of the liver is removed from rats, the ribonucleotide reductase activity of the regenerating tissue increases to 20 times the normal value between 20 and 50 h after the operation[42,43], and the deoxyribonucleotide pools show a pronounced increase at the same time[108]. In the brains of chick and rat embryos, a pronounced maximum of this enzyme activity roughly coincides in time with the fastest proliferation of neuroblasts[47].

The key function of the ribonucleotide reductase for cell growth becomes even clearer when its activity (or the size of the dNTP pools) is followed during the division cycle and is compared with the DNA synthesis in cultures of synchronized cells. In mouse L cells[41] and (particularly clearly, see Fig. 6) in yeast cells[109], the ribonucleotide reductase reaches its peak shortly before the strongest DNA production during the S phase (*i.e.* the synthesis phase between two cell divisions). The quantity of the four deoxyribonucleotides present in synchronized mammalian cells (mouse, hamster)[6-9] also increases by a factor of 10 only during the S phase and decreases in the early G2 phase, during or shortly after the DNA synthesis reaches its maximum.

From the action of inhibitors of mRNA and protein biosynthesis such as actinomycin[43], puromycin[35], or cycloheximide[41,109] in many of these tissues, it is quite clear that the increase and decrease in the ribonucleotide reduction is in fact due to induction or absence of *de-novo* enzyme synthesis. The early appearance of ribonucleotide reductases in growing cells can be easily reconciled with the stepwise onset of the production of mRNA, protein, and DNA[110]. On the other hand, no pronounced growth-dependent variations of this kind have been observed for preceding and succeeding enzymes such as thioredoxin reductase[100] and DNA polymerase[35,41].

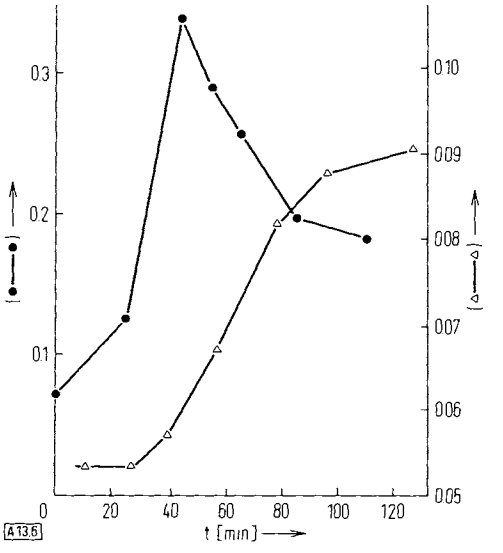


Fig. 6. Ribonucleotide reductase activity (●···●) and DNA production (△ △) in synchronized yeast cells (after [109]). Left-hand ordinate: nmol of substrate reacted per mg of protein per min; right-hand ordinate: mg of DNA per 100 ml of culture; abscissa: incubation time of the yeast culture.

Ribonucleotide reductase is just as essential for the bacterium *Escherichia coli* as for eukaryotic cells. Two mutants E101[111] and LD195[112] in which the proteins B1 and B2 of the reductase exhibit only a small fraction of the activity of the wild type and are temperature-sensitive have recently been isolated. The gene locus *dna*F (one of seven that are responsible for DNA synthesis) was thus identified as the structure gene for ribonucleotide reduetase. These bacteria can multiply at 37 to 42 °C only if deoxyribonucleosides are supplied in the medium, and growth inhibition by hydroxyurea[58] is 20 times as strong as in the case of the wild type. Similarly, coenzyme B_{12} may be limiting for the type II reductases. The nodule bacterium *Rhizobium meliloti* exhibits growth disturbances and a reduced DNA content in the cells if it lacks cobalt, the central metal atom of deoxyadenosylcobalamin[113].

Their significant involvement in the DNA synthesis and in cell proliferation makes the ribonucleotide reductases (and their inhibition) a subject of great current interest in virus-infected tissues and in tumor cells. T4 phages contain three genes *nrd*A, B, and C; phage-specific ribonucleotide reductase and thioredoxin (but not thioredoxin reductase) that have only a remote similarity to the bacterial proteins are formed in the host cell as the products of these genes[23,24,62,114]. Increased specific reductase activities are found in kidney cells infected with polyoma virus[40], in Yaba monkey virus

tumors[49], and in leukemic mice[46], but there are generally no qualitative differences in relation to normal mammalian enzymes. Until pure enzymes from normal and from infected tissues are available, it will therefore not be possible to say for certain whether pathogenic plant and animal viruses, and in particular the oncogenic RNA viruses, have specific ribonucleotide reductases. No obvious differences in the reductase systems have been found in rat tumors and healthy rat livers. Nevertheless, the reduction of ribonucleotides in tumors merits great attention from the diagnostic and chemotherapeutic standpoints, since *Elford* has been able to demonstrate a striking correlation between the rate of growth of numerous rat hepatomas and this enzyme activity[150]: The very rapidly proliferating Novikoff and Walker tumors exhibit reductase activities up to 500 times as high as those of the slowest-growing tumors. Relationships are conceivable between the cytotoxic action of hydroxyurea and arabinonucleosides for malignant and normal tissues *in vivo* and their inhibitory effect on ribonucleotide reductases *in vitro*[136, 58, 81, 115]; both substances most strongly inhibit DNA synthesis and have less effect on the RNA and protein syntheses. On the other hand, it must not be forgotten that the nucleic acid metabolism of a cell involves two dozen nucleotides and not many fewer enzymes, so that the role of an individual enzyme, though important, can hardly be the sole determining factor in a complex process like DNA replication.

6. Outlook

Numerous chemically and biologically interesting aspects of the reduction of ribonucleotides require further elucidation: reaction mechanism, structure of the active sites and mode of action of the effector molecules on the protein, initiation and repression of enzyme biosynthesis. Though the initiating factors of the enzyme induction are still completely unknown, regulatory intervention in normal and in pathological cell growth by means of these key enzymes should be feasible in the future. The existence of two entirely different ribonucleotide reductase systems for the catalysis of a fundamental metabolic reaction is remarkable. We feel that a comprehensive characterization of the ribonucleotide reduction and the thioredoxin system in other organisms at different levels of evolution is of the greatest importance in order to clarify the distribution of the enzyme types and regulation patterns. This may be expected to yield new information about the evolution and phylogenesis of life, since most models of the origin of life take no account of the transition from ribonucleotides or RNA to DNA as self-reproducing material, a step that is scarcely imaginable without enzymes[116]. Finally, the search for new, possibly more easily handled ribonucleotide reductases is of interest from the standpoint of preparative nucleotide chemistry, since it could facilitate access to modified deoxyribonucleotides from the much more readily accessible ribonucleotides. The recent rapidly growing interest in the reduction of ribonucleotides should provide an answer to some of these questions.

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[1] *S. C. Hartman* and *S. Kit* in *D. M. Greenberg*: Metabolic Pathways. Academic Press, New York 1970, 3rd Edit., Vol. 4, Chaps. 19 and 20.

[2] *W. T. Hsieh*, J. Mol. Biol. *66*, 195 (1972).

[3] *R. Werner*, Nature New Biol. *233*, 99 (1971).

[4] *A. W. Solter* and *R. E. Handschumacher*, Biochim. Biophys. Acta *174*, 585 (1969).

[5] *L. Skoog*, Eur. J. Biochem. *17*, 202 (1970).

[6] *B. A. Nordenskjöld, L. Skoog, N. L. Brown*, and *P. Reichard*, J. Biol. Chem. *245*, 5360 (1970).

[7] *R. L. P. Adams, S. Berryman*, and *A. Thomson*, Biochim. Biophys. Acta *240*, 455 (1971).

[8] *K. L. Skoog, B. A. Nordenskjöld*, and *K. G. Bjursell*, Eur. J. Biochem. *33*, 428 (1973).

[9] *R. A. Walters, R. A. Tobey*, and *R. L. Ratliff*, Biochim. Biophys. Acta *319*, 336 (1973).

[10] *E. Liss, S. Brammer*, and *H. Schmidt*, Hoppe-Seylers Z. Physiol. Chem. *354*, 682 (1973).

[11] *K. L. Skoog* and *G. Bjursell*, J. Biol. Chem. *249* (1974), in press. Accumulation in the cell nucleus during the S phase leads there to a dNTP concentration of about 10^{-3} mol/l.

[12] *H. R. Woodland* and *R. Q. W. Pestell*, Biochem. J. *127*, 597 (1972).

[13] *R. L. Blakley* and *E. Vitols*, Annu. Rev. Biochem. *37*, 201 (1968).

[14] *R. Caprioli* and *D. Rittenberg*, Biochemistry *8*, 3375 (1969).

[15] *E. Racker*, J. Biol. Chem. *196*, 347 (1952).

[16] *K. Hammer-Jespersen, A. Munch-Petersen, P. Nygaard*, and *M. Schwartz*, Eur. J. Biochem. *19*, 533 (1971).

[17] *E. Hammarsten, P. Reichard*, and *E. Saluste*, J. Biol. Chem. *183*, 105 (1950).

[18] *I. A. Rose* and *B. S. Schweigert*, J. Biol. Chem. *202*, 635 (1953).

[19] *P. Reichard, A. Baldesten*, and *L. Rutberg*, J. Biol. Chem. *236*, 1150 (1961).

[20] The classification as "2'-deoxyribonucleotide: oxidized thioredoxin 2'-oxidoreductases" (EC 1.17.4) in Enzyme Nomenclature 1972 (Elsevier, Amsterdam) seems inappropriate, since the reverse reaction of the ribonucleotide reduction on which this classification is based does not exist; moreover, they are not iron-sulfur proteins as indicated there.

[21] *P. Reichard*, Eur. J. Biochem. *3*, 259 (1968).

[22] *A. Larsson* and *P. Reichard*, Progr. Nucl. Acid. Res. Mol. Biol. *7*, 303 (1967).

[23] *O. Berglund* and *O. Karlström*, Proc. Nat. Acad. Sci. USA *62*, 829 (1969).

[24] *Y. C. Yeh, E. J. Dubovi*, and *I. Tessman*, Virology *37*, 615 (1969).

[25] *R. L. Blakley* and *H. A. Barker*, Biochem. Biophys. Res. Commun. *16*, 391 (1964).

[26] *R. H. Abeles* and *W. S. Beck*, J. Biol. Chem. *242*, 3589 (1967).

[27] *J. R. Cowles* and *H. J. Evans*, Arch. Biochem. Biophys. *127*, 770 (1968).

[28] *F. K. Gleason* and *H. P. C. Hogenkamp*, Biochim. Biophys. Acta *277*, 466 (1972).

[29] *S. Yan* and *J. T. Wachsman*, Mol. Cell. Biochem. *1*, 101 (1973).

[30] *G. N. Sando* and *H. P. C. Hogenkamp*, Biochemistry *12*, 3316 (1973).

[31] *F. K. Gleason* and *H. P. C. Hogenkamp*, J. Biol. Chem. *245*, 4894 (1970).

[32] *E. Vitols, V. A. Bauer*, and *E. C. Stanbrough*, Biochem. Biophys. Res. Commun. *41*, 71 (1970).

[33] *H. Müller, R. Wahl, I. Kuntz*, and *H. Follmann*, Hoppe-Seylers Z. Physiol. Chem. *354*, 1299 (1973).

[34] *J. R. Cowles* and *J. G. Guevara*, unpublished; *B. Hovemann* and *H. Follmann*, unpublished.

[35] *J. M. Noronha, G. H. Sheys*, and *J. M. Buchanan*, Proc. Nat. Acad. Sci. USA *69*, 2006 (1972).

[36] *M. Swindlehurst, S. J. Berry*, and *W. Firshein*, Biochim. Biophys. Acta *228*, 313 (1971).

[37] *P. Reichard*, J. Biol. Chem. *236*, 2511 (1961).

[38] *S. Murphee, E. C. Moore*, and *P. T. Beall*, Cancer Res. *28*, 860 (1968).

[39] *R. Abrams, L. Libenson*, and *M. Edmonds*, Biochem. Biophys. Res. Commun. *3*, 272 (1960).

[40] *J. Kara* and *R. Weil*, Proc. Nat. Acad. Sci. USA *57*, 63 (1967).

[41] *M. K. Turner*, *R. Abrams*, and *L. Lieberman*, J. Biol. Chem. *243*, 3725 (1968).

[42] *A. Larsson*, Eur. J. Biochem. *11*, 113 (1969); Biochim. Biophys. Acta *324*, 449 (1973).

[43] *C. D. King* and *J. L. van Lanker*, Arch. Biochem. Biophys. *129*, 603 (1969).

[44] *S. Fujioka* and *R. Silber*, Biochem. Biophys. Res. Commun. *35*, 759 (1969).

[45] *S. Hopper*, J. Biol. Chem. *247*, 3336 (1972).

[46] *S. Fujioka* and *R. Silber*, J. Biol. Chem. *245*, 1688 (1970).

[47] *S. A. Millard*, J. Biol. Chem. *247*, 2395 (1972).

[48] *E. C. Moore* and *R. B. Hurlbert*, Biochim. Biophys. Acta *40*, 371 (1960); *55*, 651 (1962).

[49] *H. L. Gordon* and *R. J. Fiel*, Cancer Res. *29*, 1350 (1969).

[50] *H. L. Elford*, *M. Freese*, *E. Passamani*, and *H. P. Morris*, J. Biol. Chem. *245*, 5228 (1970).

[51] *R. H. Yamada* and *H. P. C. Hogenkamp*, J. Biol. Chem. *247*, 6266 (1972).

[52] *O. Berglund* and *F. Eckstein*, Eur. J. Biochem. *28*, 492 (1972).

[53] *P. Reichard*, Acta Chem. Scand. *12*, 2048 (1958).

[54] *A. W. Schrecker*, *D. W. Jacobsen*, and *J. Kirchner*, Anal. Biochem. *26*, 474 (1968).

[55] *R. L. Blakley*, J. Biol. Chem. *241*, 176 (1966).

[56] *A. Holmgren*, *P. Reichard*, and *L. Thelander*, Proc. Nat. Acad. Sci. USA *54*, 830 (1965).

[57] *H. P. C. Hogenkamp*, *R. K. Ghambeer*, *C. Brownson*, *R. L. Blakley*, and *E. Vitols*, J. Biol. Chem. *243*, 799 (1968).

[58] a) *I. H. Krakoff*, *N. C. Brown*, and *P. Reichard*, Cancer Res. *28*, 1559 (1968); b) *E. C. Moore*, *ibid.* *29*, 291 (1969).

[59] *E. C. Moore*, *M. S. Zedeck*, *K. C. Agrawal*, and *A. C. Sartorelli*, Biochemistry *9*, 4492 (1970).

[60] For example in the reactions of glutamate mutase, methylmalonyl-CoA mutase, and diol dehydrase: see *H. P. C. Hogenkamp*, Annu. Rev. Biochem. *37*, 225 (1968).

[61] *N. C. Brown*, *Z. N. Canellakis*, *B. Lundin*, *P. Reichard*, and *L. Thelander*, Eur. J. Biochem. *9*, 561 (1969).

[62] *O. Berglund*, J. Biol. Chem. *247*, 7270, 7276 (1972).

[63] *E. C. Moore*, Methods Enzymol. *12a*, 155 (1967).

[64] *D. Panagou*, *M. D. Orr*, *J. R. Dunstone*, and *R. L. Blakley*, Biochemistry *11*, 2378 (1972).

[65] *N. C. Brown* and *P. Reichard*, J. Mol. Biol. *46*, 25, 39 (1969).

[66] *L. Thelander*, J. Biol. Chem. *248*, 4591 (1973).

[67] *C. L. Atkin*, *L. Thelander*, *P. Reichard*, and *G. Lang*, J. Biol. Chem. *248*, 7464 (1973).

[68] *H. L. Elford*, unpublished.

[69] *E. Baril*, *B. Baril*, *R. B. Luftig*, and *H. Elford*, unpublished.

[70] *M. Ikehara* and *S. Uesugi*, Tetrahedron Lett. *1970*, 713.

[71] *J. P. Verheyden* and *J. G. Moffatt*, J. Amer. Chem. Soc. *86*, 1236 (1964).

[72] *A. Larsson*, Biochemistry *4*, 1984 (1965).

[73] *S. David* and *C. Ronzeau*, Biochem. Biophys. Res. Commun. *43*, 46 (1971).

[74] *L. J. Durham*, *A. Larsson*, and *P. Reichard*, Eur. J. Biochem. *1*, 92 (1967).

[75] *T. J. Batterham*, *R. K. Ghambeer*, *R. L. Blakley*, and *C. Brownson*, Biochemistry *6*, 1203 (1967).

[76] *B. Fraser-Reid* and *B. Radatus*, J. Amer. Chem. Soc. *93*, 6342 (1971).

[77] *J. Retey*, *A. Umani-Ronchi*, *J. Seibl*, and *D. Arigoni*, Experientia *22*, 502 (1966).

[78] *H. Follmann* and *H. P. C. Hogenkamp*, J. Amer. Chem. Soc. *92*, 671 (1970).

[79] *H. Follmann* and *H. P. C. Hogenkamp*, Biochemistry *8*, 4372 (1969).

[80] *F. Eckstein* and *L. Thelander*, unpublished experiments.

[81] *H. Follmann* and *H. P. C. Hogenkamp*, Biochemistry *10*, 186 (1971).

[82] *R. L. Suhadolnik*, *S. I. Finkel*, and *B. M. Chassy*, J. Biol. Chem. *243*, 3532 (1968).

[83] *B. M. Chassy* and *R. L. Suhadolnik*, J. Biol. Chem. *243*, 3538 (1968).

[84] *Y. Tamao* and *R. L. Blakley*, Biochemistry *12*, 24 (1973).

[85] *W. B. Orme-Johnson*, *H. Beinert*, and *R. L. Blakley*, J. Biol. Chem., *249*, 2238 (1974).

[86] *J. A. Hamilton*, *Y. Tamao*, *R. L. Blakley*, and *R. E. Coffman*, Biochemistry *11*, 4696 (1972), and further literature cited therein.

[87] *E. Vitols*, *H. P. C. Hogenkamp*, *C. Brownson*, *R. L. Blakley*, and *J. Connellan*, Biochem. J. *104*, 58c (1967).

[88] *E. C. Moore* and *R. B. Hurlbert*, J. Biol. Chem. *241*, 4802 (1966).

[89] *E. Vitols*, *C. Brownson*, *W. Gardiner*, and *R. L. Blakley*, J. Biol. Chem. *242*, 3035 (1967).

[90] *A. Larsson* and *P. Reichard*, J. Biol. Chem. *241*, 2540 (1966).

[91] *W. Beck*, J. Biol. Chem. *242*, 3148 (1967).

[92] *T. C. Laurent*, *E. C. Moore*, and *P. Reichard*, J. Biol. Chem. *239*, 3436, 3445 (1964).

[93] *B. M. Sjöberg* and *A. Holmgren*, J. Biol. Chem. *247*, 8063 (1972).

[94] *M. D. Orr* and *E. Vitols*, Biochem. Biophys. Res. Commun. *25*, 109 (1966).

[95] *P. G. Ponqué*, *A. Baldesten*, and *P. Reichard*, J. Biol. Chem. *245*, 2363 (1970).

[96] *G. Larson* and *A. Larsson*, Eur. J. Biochem. *26*, 119 (1972).

[97] *N. E. Engström*, *A. Holmgren*, *A. Larsson*, and *S. Söderhäll*, J. Biol. Chem. *249*, 205 (1974).

[98] *E. C. Herrmann* and *E. C. Moore*, J. Biol. Chem. *248*, 1219 (1973).

[99] *L. Thelander*, J. Biol. Chem. *242*, 852 (1967).

[100] *A. Larsson*, Eur. J. Biochem. *35*, 346 (1973).

[101] *A. Holmgren*, Eur. J. Biochem. *6*, 475 (1968).

[102] *D. E. Hall*, *A. Baldesten*, *A. Holmgren*, and *P. Reichard*, Eur. J. Biochem. *23*, 328 (1971).

[103] *A. Holmgren*, J. Biol. Chem. *248*, 4106 (1973).

[104] *S. Ronchi* and *C. H. Williams*, J. Biol. Chem. *247*, 2083 (1972).

[105] *W. S. Beck*, *M. Goulian*, *A. Larsson*, and *P. Reichard*, J. Biol. Chem. *241*, 2177 (1966).

[106] *G. P. Ponqué*, *A. Baldesten*, and *P. Reichard*, J. Biol. Chem. *245*, 2371 (1970).

[107] *C. K. Liu*, *P. M. Shaffer*, *R. S. Slaughter*, *P. M. McCroskey*, and *M. T. Abbott*, Biochemistry *11*, 2172 (1972).

[108] *S. S. Söderhäll*, *A. Larsson*, and *K. L. Skoog*, Eur. J. Biochem. *33*, 36 (1973).

[109] *M. Lowdon* and *E. Vitols*, Arch. Biochem. Biophys. *158*, 177 (1973).

[110] *E.g.*, in germinating wheat *M. Dobrzanska*, *T. Tomaszewski*, *Z. Grzelczak*, *E. Rejman*, and *J. Buchowicz*, Nature *244*, 607 (1973).

[111] *J. A. Fuchs*, *H. O. Karlström*, *H. R. Warner*, and *P. Reichard*, Nature New Biol. *238*, 69 (1972).

[112] *J. A. Fuchs*, *J. Neuhard*, and *H. O. Karlström*, Eur. J. Biochem. *32*, 451, 457 (1973).

[113] *J. R. Cowles*, *H. J. Evans*, and *S. A. Russell*, J. Bacteriol. *97*, 1460 (1969).

[114] *Y. C. Yeh* and *I. Tessman*, J. Biol. Chem. *247*, 3252 (1972).

[115] See, *e.g.*, *D. B. Smith* and *H. Y. Chu*, Cancer Res. *32*, 1651 (1972), and references cited therein.

[116] Cf. *H. Kuhn*, Angew. Chem. *84*, 838 (1972); Angew. Chem. internat. Edit. *11*, 798 (1972).

[117] *G. Bjursell* and *P. Reichard*, J. Biol. Chem. *248*, 3904 (1973).

[118] *J. G. Cory*, *F. A. Russell*, and *M. M. Mansell*, Anal. Biochem. *55*, 449 (1973).

[119] *M. L. Speranza*, *S. Ronchi*, and *L. Minchiotti*, Biochim. Biophys. Acta *327*, 274 (1973).

What Do We Know about the Deeper Layers of the Earth?

By Roland G. Schwab[*]

In the last twenty years modern chemical and physical methods have done much to extend our knowledge of the Earth. Some new questions have been raised, *e.g.* the question of the bonding relationships in the Earth's interior, which make the Earth an interesting object of research to chemists as well. This progress report attempts to give a survey of the Earth's structure as seen at the present day. Naturally, special emphasis has been placed on those aspects which concern the chemist.

1. Introduction[**]

In the first place it seems useful to compare the major physical characteristics of the Earth with those of neighboring celestial bodies: Mercury, Venus, the Earth, and Mars constitute the four inner planets of our solar system. Its mass of 6×10^{27} g and an average radius of 6371 km make the Earth the largest of these planets, as can be seen from Table 1.

Table 1. Relative masses, relative radii, and densities of the four inner planets (as well as of the Moon) (after *Urey* [1]).

Planet	Rel. mass	Rel. radius	Density [g/cm³]
Mercury	0.0543	0.377	5.59
Venus	0.8137	0.957	5.12
Earth	1.0	1.0	5.515
(Moon)	0.0123	0.2728	3.34
Mars	0.1077	*ca.* 0.525	*ca.* 4.1

The ancient Greeks calculated an amazingly accurate value for the Earth's radius, while the Earth's density first became known through Newton's work. However, much time was to pass before it was possible to obtain clues about the structure and composition of the Earth's interior. Apart from a series of other physical and chemical disciplines three fields have done most during this century to advance our knowledge: 1. seismology, 2. geochemistry, and 3. modern high-pressure research (high-pressure petrology).

Seismology allows physical parameters to be measured within the Earth, and high-pressure research enables geochemical material systems existing under the conditions of pressure and temperature (P, T conditions) prevailing in the Earth's interior to be investigated experimentally. Correlation of the geophysical data with the results obtained from geochemistry and high-pressure petrology is one of the main tasks of modern Earth science research. In this connection it may be asked how reliable are statements about the deeper layers of the Earth, because direct sampling and investigation is only possible on the outermost part of the planet, *i.e.* on the crust. Neither do boreholes really help to extend out direct knowledge, as it is hardly possible to drill to depths greater than 10 km. Furthermore, the means of doing so are generally only available for commercial purposes, *e.g.* for the search for oil and gas. This means, in turn, that sedimentary strata are practically the only ones penetrated. Some important clues about regions to a depth of approx. 100 km are provided by volcanic phenomena. However, insofar as science will only take as certain what can be directly observed and examined, such data can only be obtained about the Earth's surface, where there is a possibility of representative sampling.

Similarly to the situation in chemistry and physics, reliable statements may be obtained beyond this point on the basis of indirect measurements. The Earth models developed analogously to the atomic models are basically as certain as the existence of the electron or the atomic nucleus. The important role played by electromagnetic waves in the elucidation of the structure of matter has been taken over by "seismic waves" in investigations into the interior of the Earth.

2. Underlying Principles and Classical Results of Seismology

Seismic measurements concern the transmission of elastic compressions and deformations produced in the Earth by earthquakes or nuclear explosions. Fundamentally two types of oscillations can be distinguished:

1. compression waves (longitudinal oscillations) and
2. shear waves (transverse oscillations).

The velocities v_l and v_t of these three-dimensionally propagating body waves depends on the elastic properties and the density of the medium:

$v_l^2 = (K + \frac{4}{3}\mu)/\rho$ for the longitudinal waves
and
$v_t^2 = \mu/\rho$ for the transverse waves
K = bulk modulus, μ = modulus of rigidity, ρ = density

Both types of waves are produced simultaneously in solid materials; in liquids and gases, which offer no resistance to deformations, the shear waves do not arise. This offers a possibility of recognizing molten regions in the Earth's interior.

According to the above equations the velocity of the longitudinal waves is greater than that of the transverse waves by a factor of 1.7. Therefore, if one records the waves arriving at a given locality a certain distance from an earthquake focus, the longitudinal compression waves arrive as the primary waves (P-waves) and the transverse shear waves as secondary waves (S-waves). Since the density ρ increases with increasing

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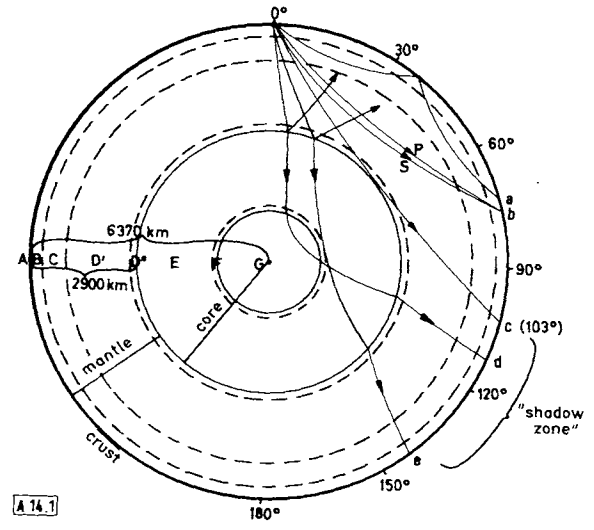


Fig. 1. Course of earthquake waves through the Earth: unless stated to the contrary, these are P waves. Deeper layers are recorded with increasing angular distance between the recording point and the focus; reflection and refraction take place at phase boundaries. The S waves disappear above 103°; P waves can only be observed if they traverse the inner core ("shadow zone" from c to e). The course and the velocity of the seismic waves have led to division of the Earth into crust, mantle, and core, and to the further subdivision of these into zones ("Bullen zones": A—G).

depth on account of rock compaction, the body waves follow a convex path relative to the center of the Earth, *i.e.* they reappear at a fixed distance from the earthquake focus. The greater the distance between the recording point and the earthquake focus, the deeper the layers that have been penetrated (cf. Fig. 1).

If the seismic waves encounter material or phase boundaries during their passage through the Earth, the respective "rays" are split up into P and S waves in addition to being reflected and refracted, so that the seismograms adopt fairly complicated forms. Earthquake waves arriving at the surface are reflected, but they also give rise to surface waves, *i.e.* disturbances which propagate two-dimensionally over the Earth's surface. Surface waves are divided into Rayleigh waves and Love waves, depending on whether their direction of oscillation is perpendicular to the surface, as is the case with water waves, or whether it is along the surface. Both disturbances appear in seismograms with maximum amplitude (M waves). Classical seismic analysis is based on plotting velocity profiles

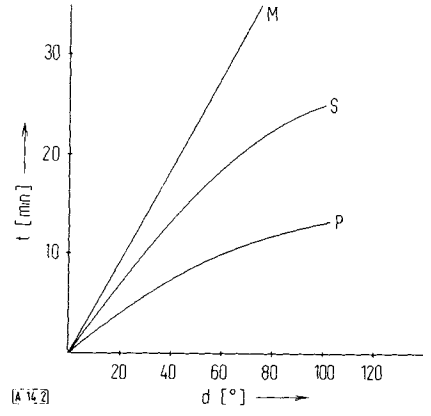


Fig. 2. Schematic representation of travel-time curves for P, S, and M waves. The curves are obtained by recording the arrival times at increasing distances (angular distance d) from the earthquake focus.

through the Earth, which can be obtained by complicated calculations from the travel-time curves. Such curves (Fig. 2) are obtained by relating the arrival times of the respective wave types to the distance from the earthquake focus.

Travel-time curves of this type reveal some characteristic features (Fig. 2):

1. For P and S waves they are curved concavely against the d-axis (d = angular distance), *i.e.* the velocity of propagation of the body waves increases with increasing distance or with increasing depth of penetration.

2. For angular distances greater than 103° P waves are seldom recorded, S waves not at all; the travel-time curve for the S waves stops slightly before 103°, as their course deviates somewhat from that of the P waves.

3. The surface waves (M waves) produce straight lines in the travel-time curves, as they propagate at constant velocity which depends upon their wavelength. Evaluation of surface wave measurements only became possible by the use of computers.

3. The Layered Structure of the Earth—A Result of Classical Seismology

Early on it was found necessary to divide the Earth into crust, mantle and core in order to evaluate the travel-time curves of body waves. The first clues pointing to the existence of a central core were provided in 1906 by *Oldham*[2]. In 1909 *Mohorovičić*[3] drew attention to the sudden increase in the velocity of body waves at a depth of *ca.* 30 km. This discontinuity of "Moho" boundary marks the boundary between the crust and the mantle. Its depth, and consequently the thickness of the solid crust, varies strongly from place to place (Fig. 3).

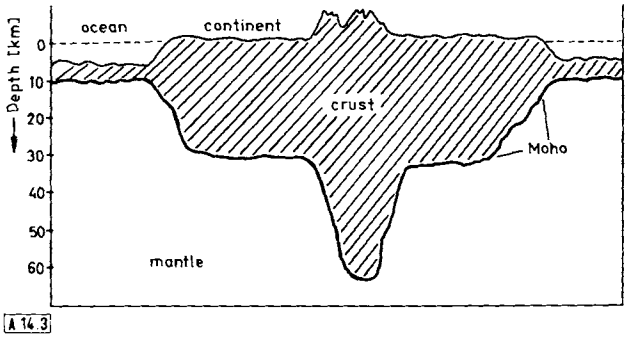


Fig. 3. Schematic representation of the crust thickness of oceanic and continental areas, corresponding to varying depth of the Moho surface. The thickness of the crust in oceanic regions is on average 5 km, rising to 33 km in continental regions. Below high mountain ranges it reaches a thickness of more than 60 km.

According to *Jeffreys*[4], the transition from mantle to core is to be expected at a depth of 2898 ± 3 km. The large central core is distinguished by strikingly different elastic properties. Thus, the P waves are retarded within the outer core, and the seismic rays refracted into it. This results in the "shading effect" of the core at angular distances of 103° to *ca.* 142°. In this area only P waves are encountered, which pass through the inner part of the core and are there strongly bent (Fig. 1). The complete disappearance of the shear waves indicates that the outer core is liquid, while a solid state of aggregation

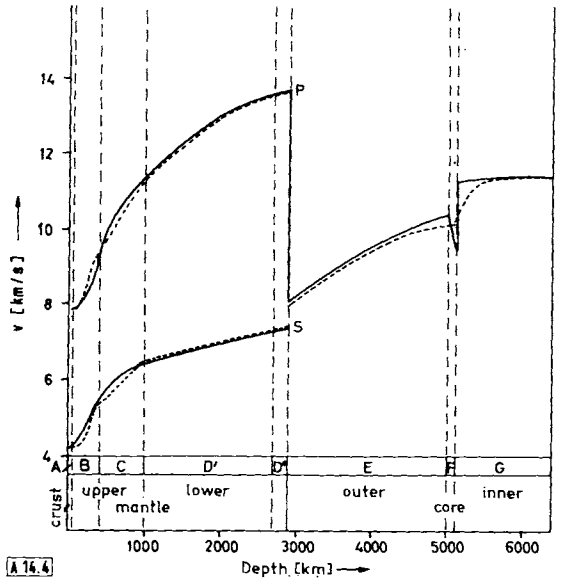


Fig. 4. Seismic profiles according to *Jeffreys* [4] (·····) and *Gutenberg* [8] (– – –). The velocity distribution of the P and S waves (v = velocity) led *Bullen* [7] to a finer subdivision of the Earth into eight characteristic zones.

must again be assumed for its inner part[5-7]. With *ca.* 68.5 wt-% the mantle constitutes the major part of the Earth's mass, followed by the core with *ca.* 31.0 wt-%. The crust accounts for less than 0.5 wt-%.

The division of the Earth into three major zones is also reflected in the classical seismic velocity profile given by *Jeffreys*[4] (Fig. 4).

On the basis of *Jeffreys*' data the Earth is divided into eight Bullen zones[6, 7] (Table 2).

Table 2. The "Bullen zones".

Bullen zone	Depth [km]	Name
A	0--33	Crust
B	33--410	Upper mantle
C	410--1000	
D'	1000--2700	Lower mantle
D''	2700--2900	
E	2900--4980	Outer core
F	4980--5120	Transition zone
G	5120--6371	Inner core

The question now is, by what phases and rocks can one most easily explain the seismic velocities observed in the respective Bullen zones. For this purpose the seismic profiles must be refined and the p,T relationships and the chemical compositions in the interior of the Earth must be studied more closely.

4. Recent Seismic Results

Recent investigations on surface waves and natural oscillations of the Earth, which can be observed during major earthquakes, have produced more reliable information about the density distribution within the Earth and have also led to more refined seismic profiles. In the upper mantle, in particular the classical views have undergone a whole series of important changes. Most authors agree on the following points (Fig. 5): the upper mantle contains a zone in which the velocity of the shear waves (S waves) in particular is markedly reduced. This low-velocity zone (LVZ) appears over the entire world at a depth of *ca.* 100 to 250 km. Its existence was first suggested by *Gutenberg*[9, 10]. It is also agreed that there are at least two clear higher-velocity zones in the upper mantle, located at 300—400 km and at 600—700 km and associated with corresponding density jumps. A further discontinuity is probably situated at a depth of 1050—1150 km. This region of the mantle (400—1050 km) is also described as a "transition zone". The data concerning the velocity and density distributions in the lower mantle are relatively consistent. Essentially, there only remain discrepancies about the nature of the transition zone between the mantle and the core from a depth of approximately 2800 km, and about the exact size of the core. Generally, the core is thought to begin at a depth of 2898 (approx. 2900) km. According to individual authors, however, this depth can be as little as 2821 km.

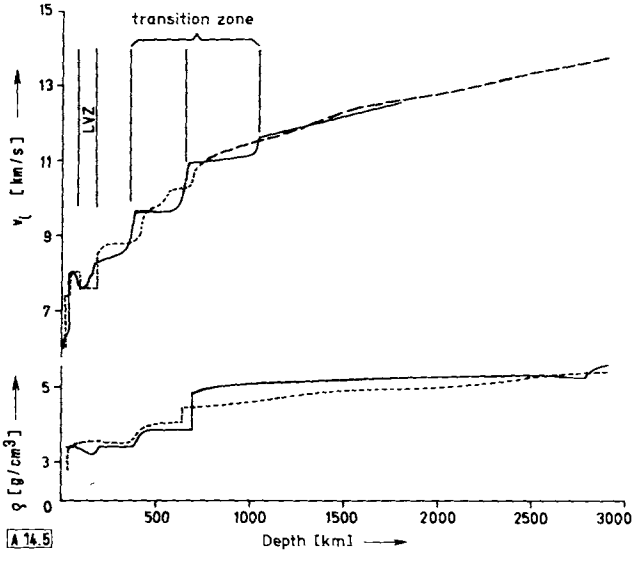


Fig. 5. Velocity of the P waves (v_l) and densities within the mantle. After the increase in the "Moho" (depth 30 km), the characteristic points are the sudden decrease of the seismic velocities in the LVZ and the stepwise velocity increases in the transition zone (according to *Archambeau et al.* [13] (·····), *Helmberger* and *Wiggins* [14] (– – –), and *Vinnik* and *Nikolayev* [15] (·– ·– ·)). The seismic velocities can be relatively well correlated with the densities (according to *Anderson* [11] (——) and *Jordan* and *Anderson* [12] (– – –)).

In the core itself, only the liquid state of the outer core and the solid state of the inner core can be taken for certain. However, it has been suggested that there are up to four layers in the core[16]. The lithostatic pressure at the relevant depth can easily be calculated from the density distribution. The pressure rises from 1 atm at the ground surface to more than 3000 kbar (1 kbar = 1000 bar; 1 bar ≙ 0.99 atm) in the core (see Fig. 6).

5. The Chemical Composition of the Earth

The seismic velocities and the corresponding densities can only be interpreted if we have some indications about the chemical composition of the crust, the mantle, and the core. It is then possible to study the corresponding systems experimentally at the appropriate temperatures and pressures. All the phenomena in the velocity and density distributions that

cannot be ascribed to the effect of compaction of the layer in question must be attributed to changes in phase or in the chemical composition. High-pressure experiments can now be performed under static conditions up to and around 450 kbar at room temperature and up to around 300 kbar at 1200 °C[17]. Under dynamic conditions (shock wave experiments) the entire pressure range prevailing in the Earth can be covered experimentally. It is therefore necessary to know the chemical composition as precisely as possible in each case.

It is generally agreed that the chemical composition of the Earth was determined by the nature of its formation, and that the solar system and the Earth arose jointly from a cloud of gas and dust, the Earth by aggregation of the solid components. There are three indications for the chemical composition of the original substance:

1. distribution of the elements expected from nuclear synthesis;
2. distribution of the elements in the Sun; and
3. the results of chemical investigations on meteorites, if possible on material that may contain still unchanged aggregations from the original dust cloud.

These sources indicate that the Earth had an original composition such as we find in certain stony meteorites (carbonaceous chondrites of type I). The main constituents of these are listed in Table 3.

Table 3. Main constituents of carbonaceous chondrites of type I (after *Wiik* [18]).

Constituent	wt-%	Constituent	wt-%
H_2O	19.29	P_2O_5	0.35
C	3.97	K_2O	0.07
organic matter	5.53	CaO	1.56
Na_2O	0.74	TiO_2	0.07
MgO	15.96	Cr_2O_3	0.34
Al_2O_3	1.64	MnO	0.22
SiO_2	22.63	FeO	10.42
NiO	1.29	FeS	16.73
		CoO	0.06

The original solid material out of which the Earth was formed in the solar system, could therefore be more simply described as silicate-iron oxide dust with relatively high proportions of ice and carbon. It is widely agreed that this original material must have passed through a high-temperature reduction stage during aggregation. The only point on which there is disagreement is whether this occurred in one original body (*Ringwood*'s one-stage theory[19, 20]) or in several smaller bodies (*Urey*'s multistage theory[21–27]). In any event, the result was the reduction of iron oxide to metallic iron. The carbon present in the original material, or the organic substance, is supposed to have acted as the reducing agent. The temperatures necessary for the reduction process are thought to have been provided by the kinetic energy of infalling dust particles and larger fragments.

The reducing conditions at temperatures above 1000 °C led to a selective depletion of the most volatile elements and to a corresponding accumulation of less volatile ones, such as Ca, Mg, Al, Si, Ti (as oxides) and Fe, Co, and Ni (as elements).

The resulting silicate-metal phases, whether in one original body or several, were gravitationally unstable and gradually underwent segregation so that the heavy metal concentrated at the center and formed the planet's core, whereby the gravitational energy was set free. According to this theory, therefore, a mantle composed mainly of Mg and Fe silicates must have been formed in addition to a metallic core composed essentially of iron and a crust whose weight was of no real consequence.

The chemical models of the mantle, which incidentally comprises the major part of the Earth (*ca.* 68 wt-% and 90 vol-%), agree on the following points:

1. More than 90 wt-% of the mantle can be described by the $MgO—FeO—SiO_2$ system; no other oxide amounts to more than 4 wt-%.

2. The constituents $Na_2O—CaO—Al_2O_3$ together form between 5 and 10 wt-%, so that approximately 98 wt-% of the mantle can be covered by the six-component system $MgO—FeO—SiO_2—Na_2O—CaO—Al_2O_3$.

3. No other oxide reaches 0.6 wt-%. Since MgO and FeO are interchangeable in most silicates, and the same holds true to some extent for Na_2O and CaO, the mantle can then be described more simply by the quaternary system $CaO—MgO—Al_2O_3—SiO_2$.

The mean atomic weights found by a seismic equation of state as proposed by *Anderson*[11, 28, 29] are consistent with this picture. This equation is based on the seismic parameter Φ, which is obtained in accordance with

$$\Phi = K/\rho \quad \text{(a)}$$

$$\Phi = \partial p/\partial \rho \quad \text{(b)}$$

$$\Phi = v_l^2 - K(4/3)v_t^2 \quad \text{(c)}$$

(K = modulus of rigidity, ρ = density, p = pressure, v_l = longitudinal-wave velocity, v_t = transverse-wave velocity)

and from seismic data (c), static high-pressure experiments (a and b) and shock-wave experiments (b) (see also Section 2). From this one can estimate the mean atomic weight in the upper and lower mantle to be 22.4. *Birch*[30] arrived at the same result by a different route.

For the outer core the values are between 45.7 and 53.2. For comparison, the atomic weight of iron is 55.85. These considerations, therefore, also indicate an iron core and an Mg, Fe silicate mantle.

Before considering the phases of the crust, mantle, and core in greater detail, we must first discuss another important parameter, *i.e.* the temperature prevailing in the respective zones.

6. Temperatures in the Earth's Interior

While it is possible to obtain precise information about the distribution of pressure within the Earth, the same cannot be done for the temperature. We can only indicate boundary conditions, which essentially are based on measurements of the heat flux through the Earth's surface and on the respective solidus temperatures, as well as on the state of aggregation in the individual layers.

In both oceanic and continental areas the mean heat flux is

$f = 1.5 \times 10^{-6}$ cal cm^{-2} s^{-1}

If we take as a basis an average heat conductivity of the rocks equal to:

$c = 5 \times 10^{-3}$ cal cm^{-1} s^{-1} °C^{-1}

The result is a "geothermal gradient" of 3 °C/100 m. This means that we could expect 3000 °C at a depth of 100 km. However, seismic data indicate that practically the entire mantle must be crystalline, while only the metallic outer core is liquid. So the solidus temperatures of the mantle silicate are generally not exceeded. This leads us to estimate the temperatures at the core-mantle boundary as around 4000 °C. However, as proved by numerous volcanoes ejecting rock melts, the solidus temperatures can be exceeded within the upper mantle, at least locally. In the light of these circumstances, a steep temperature rise is produced in the crust and the upper mantle, followed by a very level course in the rest of the Earth (Fig. 6).

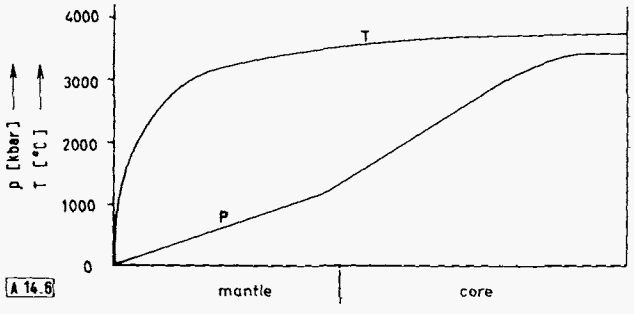


Fig. 6. Pressure and temperature distributions within the Earth

The exact position of the geotherms in the crust and the upper mantle depends upon a number of factors. These include the thermal prehistory of the Earth, the electrical and thermal conductivity of the respective layers, the precise geochemical element distribution, the nature and extent of the heat production, and the mechanism of the heat transfer.

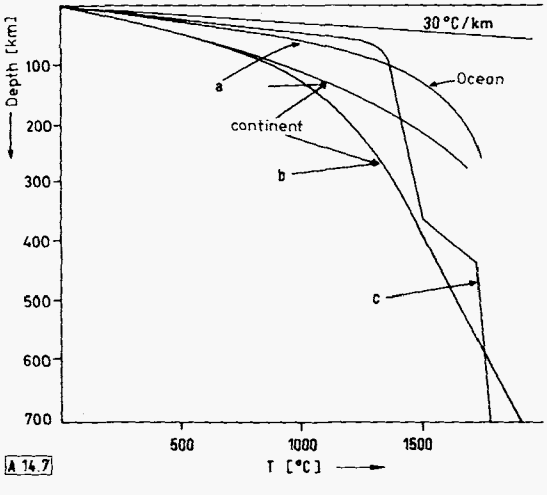


Fig. 7. Course of geotherms in the upper mantle according to *Ringwood* [20] (a), *Clark* and *Ringwood* [31] (b), and *Turcotte* and *Oxburgh* [32] (c). The differences between ocean and continent should be observed, as well as the almost constant temperature relationships as they are assumed to be at a depth of *ca.* 100–400 km on account of convection (c). The theoretical gradient of 30 °C/km is also given; this was found from measurements of the heat flux through the crust.

A further decisive factor is to what extent convection is possible. After all, very different geotherms are given for the upper mantle, which however come markedly closer to one another with increasing depth (Fig. 7).

The course of the geotherms reveals that the greater part of the Earth's heat is produced in the crust and the upper mantle. The reason for this is that the natural radioactive elements are strongly concentrated in the crust and the upper mantle, being almost completely absent in the rest of the Earth. We shall now discuss in greater detail the phases and rocks one can expect to find in the respective zones.

7. The Crust

The chemical and mineralogical composition of the crust with its directly accessible rocks is well known. The oceanic crust consists of a layer of deep sea sediments *ca.* 1 km thick and below it of a dark, magmatic rock, named basalt. Basalt is made up essentially of Ca, Mg, Fe metasilicates (pyroxenes) and Ca, Na aluminosilicates of the $NaAlSi_3O_8$—$CaAl_2Si_2O_8$ system, the plagioclases. Corresponding lavas are also ejected from the majority of the 800 or so volcanoes active at the present time, in both oceanic and continental regions.

On the basis of seismic data and field observations we can assume that the lowest part of the continental crust is also basaltic. The upper part of the continental crust is basically determined by the reactions of the rocks with the atmosphere *i.e.* by weathering and sedimentation. Sinking of the sediments into the *p,T* region of the middle crust produces first consolidation (diagenesis), then solid-state reactions with the formation of new minerals (metamorphosis), and finally partial melting (anatexis).

We know from investigations on these systems that the primary eutectic melt is very water-rich and that it has a granitic composition. In the resulting magma chambers convective flows occur, tearing material off the roof and the walls of the magma chambers. This material is totally or partially melted, while crystallization occurs on the bottom. This process causes the magma chambers to ascend until they finally solidify near the surface as large granite domes. Later they are exposed by erosion and again transformed into sediments. The continental crust therefore reveals a layer structure (Fig. 8). Rock melts can be expected in the middle part of the crust; however, these are very rich in SiO_2 (acidic). The magmas of the crust are granitic and only occur in the continental region.

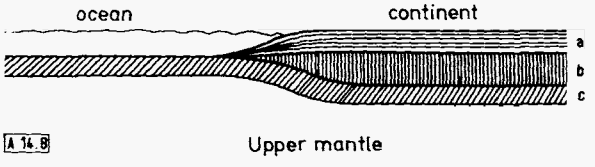


Fig. 8. Schematic representation of the layer structure of the continental crust. Key: a = Sediment, b = granite and gneiss, c = basalt/gabbro.

Basaltic melts can not be generated in the crust region, as can easily be seen by comparing the melting ranges of granites and basalts with the *p,T* conditions prevailing in the crust and the upper mantle (Fig. 9). Within the variation range of the geotherms, granitic melts may form from a depth of *ca.* 20 km if appropriate starting material is available. Basaltic melts cannot form either in the crust or in the mantle without

the presence of H_2O. However, if water is present basaltic melts can be generated under the conditions of the upper mantle. Beside the granitic magmatism of the crust, therefore, we have the basaltic magmatism of the upper mantle.

The basalt magmas from the mantle can provide important information about this part of the Earth. However, the chemical composition of the melts may undergo appreciable changes during their ascent on account of fractional crystallization and/or absorption of crust material (assimilation). Oxidation processes and separation of oxidic iron ores may lead to acidic residual melts.

Part of the basaltic melts does not solidify into true basalt at the Earth's surface but rather deeper down, *e.g.* in the lower crust. Under the cooling conditions prevailing here the melts take a long time to crystallize and are of a special texture. The special name of "gabbro" is given to the basaltic magmas solidifying at such greater depths.

It would, therefore, be more correct to describe the lower crust as gabbroid. This raises the question of how to explain the transition from the crust to the mantle in the Moho; is the Moho surface a phase boundary or a chemical boundary?

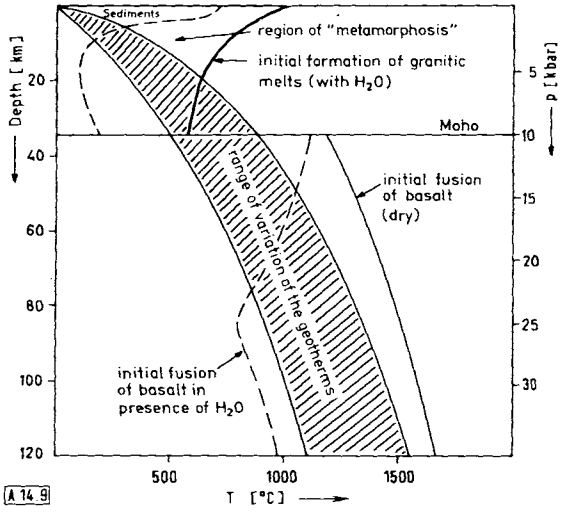
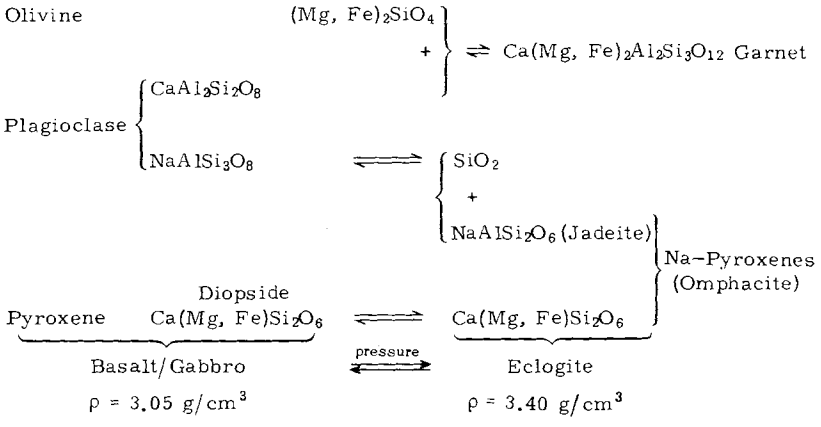


Fig. 9. The possibilities for the formation of rock melts in the crust and upper mantle. Basaltic melts can only be formed in the upper mantle and in the presence of H_2O; granitic magmas are formed in the crust. Metamorphic rocks are also formed here.

8. The Mantle

8.1. The Nature of the Moho Discontinuity

In accordance with the chemical composition of the mantle one can expect to find essentially Mg,Fe silicates below the Moho. It is interesting to find that only two types of rock satisfy the geophysical requirements as regards composition, density, mineral constituents, *etc.* Both rocks consist basically of metasilicates and orthosilicates. The first rock type, eclogite, is formed directly from basalt under a pressure of *ca.* 15 kbar at 1000 °C. It then undergoes an isochemical phase transformation in which the loosely packed framework structures of the feldspars, in particular, change into the denser mineral phases of orthosilicates and metasilicates. The reaction can be formulated in the manner shown in Scheme 1.



Scheme 1

The conversion of basalt or gabbro into eclogite leads to a marked increase in the density, which provides a good explanation for the velocity increase of seismic waves as they reach the Moho discontinuity. However, there exists no general agreement on the course of the transformation region in the p,T diagram, especially at lower temperatures[33,34]. If one assumes the Moho to be a phase boundary between gabbro and eclogite[33,35-39], then the basaltic magmas would be formed by complete melting of this "mantle rock".

Peridotite offers a second possibility of a mantle rock, with olivine as the orthosilicate in place of garnet. Peridotite differs chemically from basalt, so that in this case one should describe the Moho as a chemical boundary. It must be possible for a basaltic magma to form from the peridotite of the upper mantle by fractional melting. *Ringwood*[40] describes such a peridotite as "*pyrolite*". The concept of a peridotite mantle is supported by a series of geological and petrographic observations[41,45,31]. A pyrolite made up of basalt and dunite in a ratio of 1:3 would offer a good explanation for the oceanic heat flux and the seismic velocities; on the other hand, a corresponding chemical composition is also expected on the basis of the "chondritic earth model" (Table 4).

There are several arguments against the Moho being a pure phase boundary. Here we shall only point out that at a phase boundary there ought to be a strong correlation between the heat flux, which naturally depends on the temperature at the respective depth, and the position of the Moho, *i.e.* the crust thickness. But since the heat flow is the same in the oceanic region as in the continental, there is then no

explanation for the great differences between the thickness of oceanic and continental crust. There are also geochemical reasons for regarding an eclogite mantle as an extremely unsatisfactory hypothesis[47], though one can, of course, always

Table 4. Composition of the mantle rock (after *Green* and *Ringwood* [46]) in wt-%, and definitions of some important rock names.

	Derived as pyrolite	Derivation from the "chondritic earth model"
SiO_2	43.06	44.69
MgO	39.32	39.08
FeO	6.66	7.81
Fe_2O_3	1.66	--
Al_2O_3	3.99	4.09
CaO	2.65	3.19
Na_2O	0.61	1.14

Eclogite:	consists mainly of pyroxene (metasilicate) and garnet (orthosilicate); it is the high-pressure equivalent of basalt
Peridotite:	contains more than 90% of pyroxene + olivine (orthosilicate)
Dunite:	contains more than 90% of olivine
Pyrolite:	a special peridotite having the composition dunite: basalt = 3 : 1 (mantle peridotite).

count on eclogite being present in the upper mantle. Basaltic melts resulting from partial fusion of the peridotite mantle are supposedly transported into the p,T range of eclogite formation, particularly in tectonically active regions, and are correspondingly transformed. In this manner mantle regions with eclogite layers in the peridotite rock occur[48]. One can therefore conclude that there is a peridotite mantle of pyrolite composition with eclogite layers showing strong lateral variations. If this assumption is correct, then the seismic discontinuities of the mantle must be capable of correlation with the phase changes of the mantle rock which occur under the corresponding p,T conditions.

8.2. Phase Transformations in Peridotite with Increased Pressure and Temperature

If we assume that the mantle peridotite also contains Na_2O, CaO, and Al_2O_3, then at 1 atm a framework silicate, namely Na-Ca feldspar (plagioclase) appears as an aluminum carrier. The rock is then referred to as plagioclase-peridotite. As is the case with the plagioclase of basalts, the loose framework structure becomes unstable on elevation of pressure and reacts with olivine (formally) in accordance with

$$3Mg_2SiO_4 + 2CaAl_2Si_2O_8 \rightleftharpoons MgAl_2O_4 + \underbrace{MgAl(Si,Al)O_6 + Mg_2Si_2O_6 + 2CaMgSi_2O_6}_{\text{Al-pyroxenes}}$$

olivine — plagioclase — spinel

A spinel peridotite with Al pyroxenes is therefore formed from the plagioclase peridotite. As the pressure is increased further there is another increase in density: a garnet phase is formed through the reaction of the pyroxene with the spinel, formally according to

$$4MgSiO_3 + MgAl_2O_4 \rightleftharpoons Mg_3Al_2Si_3O_{12} + Mg_2SiO_4$$

pyroxene (enstatite) — spinel — garnet (pyrope) — olivine (forsterite)

The spinel-peridotite changes over into garnet-peridotite.

On account of its importance for ground-surface phenomena, the low-velocity zone (LVZ) of the seismic profiles between 100 and 250 km will be dealt with separately later on. We must therefore examine whether the sudden velocity jumps of the seismic waves at depths of *ca.* 400 km and *ca.* 650 km coincide with the density increase reactions of the mantle peridotite in corresponding regions of temperature and pressure. Garnet-peridotite remains stable to a depth of around 400 km. Beyond this depth two densification reactions can be demonstrated experimentally according to *Ringwood*[49]. These are:

1. Conversion of olivine $(Mg, Fe)_2SiO_4$ into a high-pressure phase of the type of spinel, in which, however, the Si^{4+} is still tetracoordinated:

$$(Mg,Fe)_2^{[6]}Si^{[4]}O_4 \xrightarrow{p} \beta(Mg,Fe)_2^{[6]}Si^{[4]}O_4$$

olivine type — spinel type

$\Delta\rho = 8\%$

and

2. Decomposition of the metasilicate (pyroxenes) into complex garnets, in which a quarter of the Si^{4+} present changes over to six-fold coordination, *e.g.*

$$2Mg_2^{[6]}Si_2^{[4]}O_6 \xrightarrow{p} Mg_3^{[6]}(MgSi)^{[6]}Si_3^{[4]}O_{12}$$

pyroxene — garnet

$\Delta\rho = 10\%$

Since olivine constitutes *ca.* 57% of the mantle peridotite, and pyroxene *ca.* 25%, we have an explanation for the density jumps and the associated velocity increases of seismic waves at a depth of *ca.* 400 km. Experimental results indicate the existence of two seismic discontinuities lying close together between 360 and 420 km, and this has been confirmed by more recent measurements[50, 51].

Thermodynamic arguments based on germanate model systems as well as shock-wave experiments suggest that the densification reactions shown in Scheme 2 start in the second and larger seismic discontinuity at a depth of *ca.* 650 km:

1. $(Mg,Fe)_2SiO_4$ (spinel) $\begin{cases} \xrightarrow{p} (Mg,Fe)_2SiO_4 \text{ of the } Sr_2PbO_4 \text{ type} \\ \text{or} \xrightarrow{p} (Mg,Fe)SiO_3 \text{ of the ilmenite type} + (Mg,Fe)O \end{cases}$

2. $M_3(M,Si)Si_3O_{12}$ (garnet) $\begin{cases} \xrightarrow{M=Mg^{2+}} 4MSiO_3 \text{ of the ilmenite type } (FeTiO_3) \\ \left[\xrightarrow{M=Ca^{2+}} 4MSiO_3 \text{ of the perovskite type } (CaTiO_3)\right] \end{cases}$

3. $NaAlSi_2O_6 \longrightarrow NaAlSiO_4$ of the Ca_2FeO_4 type + SiO_2 (stishovite)
jadeite

Scheme 2

These transformations result in hexacoordination of the entire Si^{4+}, which is associated with a considerable density jump. The normal density ρ_0 of the rock formed here lies between 3.99 and 4.03 g/cm^3. It is approximately equal to that of the corresponding isochemical mixture of the free oxides in which $Si^{[6]}O_2$ in the rutile type is present as stishovite. At deeper seismic discontinuities one must therefore assume the possibility of a transformation into still denser phases.

Indeed there is at least one other clear seismic discontinuity at a depth of 1050 km. Beyond that, however, the seismic profiles of the lower mantle permit no major density changes. Even in the case of the discontinuity at 1050 km we had to consider densification reactions of the silicates to compounds with a density 5% above that of the free oxides. Mg^{2+} and Fe^{2+} must then adopt a coordination number higher than 6; a possibility would be, for example, the conversion of $MgSiO_3$ (of the ilmenite type) into a perovskite structure and of Mg_2SiO_4 (of the Sr_2PbO_4 type) into a K_2NiF_4 and/or a Ca_2FeO_4 structure. Here the Si^{4+} is still hexacoordinated but the Mg^{2+}(Fe^{2+}) has a coordination number of 12.

8.3. The Lower Mantle

It is likely that this does not exhaust the possibilities of further phase transformations. The lower mantle is supposed to be "squeezed" at the boundary with the core into a state of densest atomic packing. Up to now a mantle of chemically uniform composition has been assumed, with $X_{FeO} = ca.\ 0.1$[31], an opinion not shared by some geophysicists[38, 51] who regard the lower mantle as having an iron concentration that increases with increasing depth. Recent seismic measurements by *Johnson*[52] (Fig. 10) point to the existence of further phase transformations, which contradict the homogeneity[31, 53, 54] assumed up to now for this region.

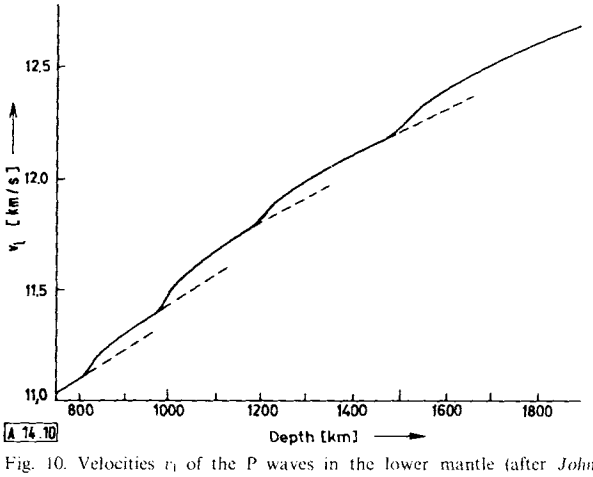


Fig. 10. Velocities v_l of the P waves in the lower mantle (after *Johnson* [52]). The inhomogeneities established can probably be attributed to further phase transformations with smaller density jumps. In any case, the normal density ρ_0 of the lower mantle must clearly be above that of oxide mixtures of peridotite of pyrolite composition.

The experimental interpretation of the phase relationships in the lower mantle is based essentially on shock wave experiments[55, 56]. It can be shown that under the corresponding p,T conditions the densities are higher than those of the free oxides. The experiments also indicate further phase transformations in the lower mantle, although an increase in the iron content cannot in principle be ruled out. On the basis of crystallochemical arguments, essentially minerals of the perovskite and calcium ferrite types can be expected.

9. The Core

The Wiechert-Gutenberg discontinuity defining the core is certainly a chemical boundary. According to an alternative hypothesis proposed by *Ramsay*[57, 58], the boundary between the mantle and the core is an isochemical phase boundary due to pressure degeneration of the mantle silicate, but the existing geophysical and geochemical evidence argues strongly against this view[59].

Thus, the relationships obtained experimentally between the density, pressure, seismic velocities, and mean atomic weights show that a mantle material of Mg, Si, and O in a metallic state could not satisfactorily explain the densities and seismic velocities determined for the core. Furthermore, the transformation of nonmetals into a metallic state under high-pressure conditions is only accompanied by greater volume or density changes (>20%) if the nonmetal has an "open" structure with directional covalent bonding. The density increase then results from the denser packing of the metallic state. It must be assumed, however, that in the lower mantle the silicates are already as densely packed as possible. According to *Ramsay*'s hypothesis, on transition to the metallic state this already highly compressed material must undergo a first-order transformation (as a multicomponent system) accompanied by a density jump of around 65%. However, the experimental and theoretical results to date show this to be impossible.

If the original material of the Earth is assumed to be chondritic then transfer of the entire iron and nickel into the core would produce a central body with a mass of only 26.48% of the total, as compared with the actual figure of around 31%[20]. There must, therefore, be another element that has entered the Earth's core. Further specific evidence for this argument is given below:

If the density of the core is compared with that of iron under the corresponding p,T conditions (shock-wave experiments), it is found that the core density is 10–20% lower than the density of iron. On the other hand, the seismic-wave velocities are considerably higher in the core than in pure iron[30, 59, 60]. Finally, a mean atomic weight of between 45.7 and 53.2 has been estimated for the outer core from seismic equations of state, while the atomic weight of iron is 55.85. An element of lower density and lower atomic weight must therefore have been mixed in a fairly high proportion with iron in the core; at the same time, this would be responsible for the higher seismic velocities.

H, He, C, O, N, Mg, Si, and S have been discussed as possible admixtures. Of these, H, He, C, O, and N can be discounted, since they do not reduce the density of iron; they merely occupy the gaps present in the iron lattice. Mg is an unlikely candidate, since its affinity for oxygen is greater than that of silicon, which is also available in large amounts. Two possibilities remain therefore: admixture of S or of Si (Table 5).

Table 5. Chemical composition of the core in wt.-%.

	after *Mason* [61]	after *Ringwood* [20]
Fe	86	84
Si		11
Mg	6.0	
S	7.4	
Ni		5.3
Co	0.4	

Although no arguments can be presented which totally exclude either of the possibilities, there is strong evidence in favor of silicon as the admixture element. With iron, silicon forms

an extensive series of solid solutions with a clear reduction in density and an increase in seismic velocities. Furthermore, silicon has been proved to be an essential component of the metallic phase of enstatite-chondrites (stony meteorites)[62].

The core is therefore an iron body, which has a liquid outer part and solid inner part, and which contains large amounts of S or Si in solution, the probability being strongly in favor of Si. The Earth's magnetic field has its origin in the liquid outer core. The phases of the whole Earth are compiled in Table 6.

tion of a zone of partial melting (Fig. 11). Basaltic melts with some free H_2O (and CO_2!) are expected here, which can be observed in large quantities during volcanic activity. The top and the bottom of the LVZ prove in this case ($P_{H_2O} < P_{tot}$) to be intersections of the geotherms with the solidus line of the mantle peridotite.

Anderson and *Sammis*[63] assume that at least 1% of melt must be present to permit convective heat transport. It is their opinion that an equilibrium is set up between heating, melting and convective removal of heat by the melt. The

Table 6. Chemical and mineralogical composition of the Earth. Overall composition: Mg, Fe, Si, O with > 1% Ni, S, Ca, Al; 0.1–1% Na, K, Ti, P, Co, Mn; others: 0.1%. M = metal.

Chemical composition	Rough division	Bullen zone	Depth [km]	Phases		ρ[g/cm³]	Coordination numbers of the elements
O, Na, K, Ca, Al, Si, Ti (Ba, Sr, La, U) Th	Crust	A		sediments metamorphic rocks and granites		≈2.8	Si 4 Mg, Fe 6
			33	basalt			
Mg, Fe, Si, O (Na, Ca, Al, Ni, Cr)	Upper mantle	B	80	spinel-peridotite garnet-peridotite		≈3.38	Si 4 Mg, Fe 6
				M_2SiO_4 olivine	$2M_2Si_2O_6$ pyroxene		
			360	⇕	⇕		
			410				
	Transition zone	C	420	M_2SiO_4 spinel	$M_3(M,Si)Si_3O_{12}$ garnet	≈3.62	Si 4, 6 Mg, Fe 6
			650	⇕	⇕		
			700	M_2SiO_4 (Sr_2PbO_4 type)	$MSiO_3$ (ilmenite and perovskite type)	≈4.0	Si, Mg, Fe 6
			1000	⇕	⇕		
	Lower mantle	D′	1050	denser phases than free oxides (MO, SiO_2)		≈(4.7) 7% denser than free oxides	Mg, Fe ≥ 6 Si 6
				M_2SiO_4 (Ca_2FeO_4 or K_2NiF_4 type)	$MSiO_3$ (perovskite type) further transformations?		
			2700				
		D″	2900	densest atomic or ionic packing		≈(5.7)	
Fe, Ni, Si (S?)	Outer core	E		Fe, Ni, Si metal liquid		≈(9.7)	Mg, Fe, Si 12
			4980	⇕			
	Transition zone	F	5120			≈(12.5)	
	Inner core	G		Fe, Ni, Si metal solid			Mg, Fe, Si 12
			6370			≈(13.0)	

10. Influence of the Deeper Layers on the Geological Phenomena at the Surface

10.1. The Low-Velocity Zone (LVZ) in the Upper Mantle

In recent years special attention has been paid to the zone in the upper mantle in which the velocity of the seismic waves suddenly decreases.

If we consider all the observations and facts available[63, 64] we cannot escape the conclusion that the mantle material in this region must be partly molten. This would mean that the geotherm exceeds the solidus temperature of the mantle peridotite, which is only possible if the mantle material contains water. Even 0.1 wt-% of water leads to a displacement of the liquidus-solidus field, so that the LVZ merits the description of a zone of partial melting (Fig. 11). Basaltic melts with some free H_2O (and CO_2!) are expected here, which can be observed in large quantities during volcanic activity. The top and the bottom of the LVZ prove in this case ($P_{H_2O} < P_{tot}$) to be intersections of the geotherms with the solidus line of the mantle peridotite.

Anderson and *Sammis*[63] assume that at least 1% of melt must be present to permit convective heat transport. It is their opinion that an equilibrium is set up between heating, melting and convective removal of heat by the melt. The critical proportion of melt, leading to rapid convective heat dissipation and the associated magmatic and volcanic activity, is given as 5%. The magmatic phase lasts until the uncritical value of *ca.* 2% of melt is again reached. The ascent of the lighter magma results in the crust being formed as a fractionation product of the mantle.

While the interpretation of the LVZ as a zone containing some melt is basically correct, there are other possible explanations for its sharp boundaries, suggested by recent experimental results.

The fundamental question is, in what concentrations can H_2O and CO_2 be expected in the mantle? The enormous quantities of gas emitted by volcanoes suggest the presence of large quantities of H_2O and CO_2 (>0.1%). The top and the bottom

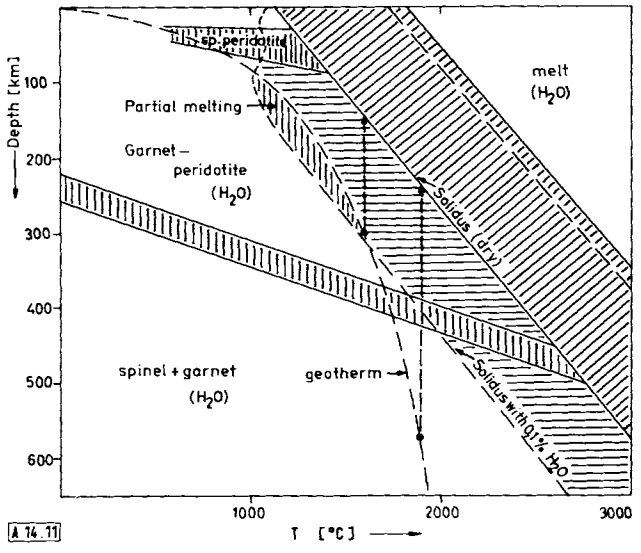


Fig. 11. The liquidus-solidus region of mantle peridotite with and without water in the upper mantle. In the absence of water the geotherm does not reach the solidus; moreover, the liquidus-solidus range is relatively narrow. Melting was only possible by the ascent of material from greater depth (arrows). Even 0.1% of water lowers the solidus temperature so much that partial melting in the LVZ area becomes possible. Since the liquidus line practically does not move at all, the field of melt equilibrium is considerably enlarged.

of the LVZ would in this case be explained by the stability of the compounds formed between the H_2O and the mantle silicates. Under moderate p,T conditions *i.e.* at temperatures up to *ca.* 1000 C and in the pressure range up to *ca.* 20 kbar, water enters the silicate at the Si^{4+} in the form of OH^- ions. Band silicates and layer silicates (amphibole, phlogopite, serpentine) are formed, which decompose into water-free silicates and H_2O at higher temperatures and pressures (Fig. 12). The resulting melting point depression determines the roof of the LVZ.

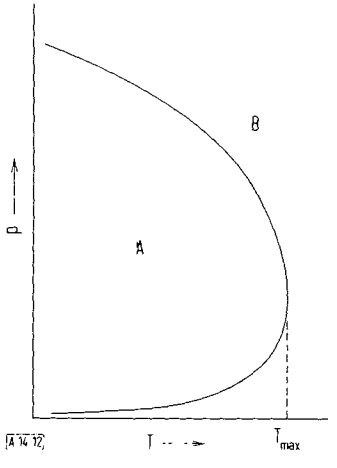


Fig. 12. Schematic representation of the stability field of water-containing silicates with OH^- ions at the Si^{4+} (A). At higher temperatures and pressures these compounds decompose into silicate and H_2O (B).

Sclar[65] was able to demonstrate that free H_2O can be reincorporated into mineral phases under the p,T conditions prevailing at the bottom of the LVZ, though it is then bound in a different manner. For example, at 40 kbar and 1200 C Mg_2SiO_4 reacts with H_2O to form a metasilicate:

$$Mg_2SiO_4 + 2H_2O \rightleftarrows Mg_2SiH_4O_6$$

This is therefore a pyroxene in which every other SiO_4^{4-} tetrahedron of the anionic chain is replaced by an $H_4O_4^{4-}$ tetrahedron. In these "water pyroxenes" we see a crystallochemical possibility of incorporating large amounts of water into the phases of the mantle, and such minerals would then make up the lower boundary of the LVZ.

Investigations on gas inclusions in fragments of mantle peridotite (olivine nodules) transported to the surface in basalt lavas led *Ernst*, *Mages*, and *Schwab*[66,67] to the conclusion that CO_2 as well as H_2O is incorporated into the mantle silicate phase. Solid solutions are presumably formed here, in which SiO_4^{4-} is replaced by CO_4^{4-} and which these authors describe as "carbon silicates".

According to *Neuhaus*[68], tetracoordination of the C^{4+} in orthocarbonate is only to be expected under high-pressure conditions (pressure homologs rule). These are supposed to lead to an adaptation of the cationic and anionic radii, resulting in ever higher coordination numbers and denser packing. Tetracoordination is possible only with a radius ratio $r_{cation}/r_{anion} \gtrsim 0.22$, for example, in the silicates at 1 atm with $r_{Si^{4+}}/r_{O^{2-}} = 0.29$. In carbonates the coordination number is 3 because $r_{C^{4+}}/r_{O^{2-}} = 0.11$. The pressures necessary for the transition to tetracoordination, when the carbonates assume a silicate-like structure *e.g.* according to

$$\underset{\text{magnesite}}{MgC^{[3]}O_3} \xrightarrow{p} \underset{\text{orthocarbonate with anionic chains}}{MgC^{[4]}O_3}$$

are estimated by *Neuhaus* to be ≈ 200 kbar for the pure phases. Markedly lower pressures can however be expected for the isomorphous substitution of Si^{4+} by C^{4+}, depending on the extent of the substitution and on the composition and structure of the silicate. Accordingly, the bottom of the LVZ could be regarded as a "bonding boundary", marking a changeover from the high-pressure chemistry of the mantle, where CO_2 and H_2O are incorporated in the crystalline phases as CO_4^{4-} and $H_4O_4^{4-}$ groups, to "normal chemistry", with the CO_2 and H_2O occurring as free molecules or in lower-coordinated mineral phases.

This interpretation of the LVZ as a zone in which the H_2O and the CO_2 released from the mantle silicates lead to partial melting also offers a possible explanation for the formation of carbonatic, basic, and acidic rock melts from one starting material[69]. The gas richness of the resulting melts would at the same time provide the power for active, sometimes explosive volcanism.

10.2. Tectonic Phenomena Caused by the Partial Melting and by Phase Transformations in the Upper Mantle

The described zone containing molten regions is less dense than the neighboring layers of the mantle and is therefore unstable both from the mechanical and the gravitational point of view. This result in the formation of convection cells in the upper mantle, which exert powerful forces on the higher-lying crust, producing stretching, compression, arching, and subsidence (Fig. 13).

Basaltic melts can ascend through fissures in the expansion zones, while earthquakes occur in the zones of compression. Within the LVZ the more volatile components collect at the "top boundary" and here produce a further reduction in the viscosity. In this way the crust and a part of the upper mantle can slide on the LVZ with relatively low friction. This explains both continental drift and the phenomenon of sea-floor spreading, *i. e.* the formation of new oceanic crust by an ascending convective current emerging from a midoceanic ridge with the resulting lateral displacement of the sea floor on both sides of the ridge[70].

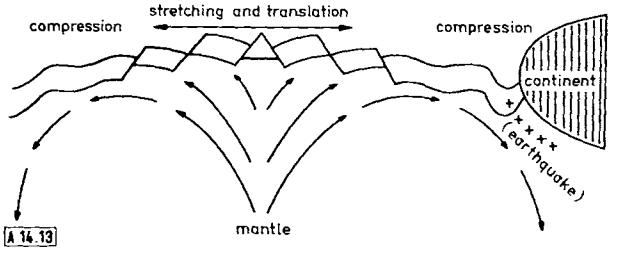


Fig. 13. Schematic representation of the effects of convection in the upper mantle. As well as arching and stretching in the ascending convection current, translation occurs by its side, followed by compression and subsidence.

Convective flows in the upper mantle are also the cause of the formation of domes and depressions, though it must be remembered that these are ultimately caused by displacements of phase boundaries due to the different temperatures in the ascending and descending parts of the convection current. The densification reactions in the upper mantle can also give rise to earthquakes, which have been recorded from depths of 700 km (maximal). The source of the energy of tectonic phenomena observed on the ground surface and the energy required for the formation of the associated crystal structures should thus be sought entirely in the upper mantle. And finally, the crust itself originates from the mantle.

11. Summary

During the last twenty years geochemical, geophysical and petrological investigations have done much to extend our knowledge of the deeper layers of the Earth. It was already known that the Earth is divided into crust, mantle, and core, and that these regions differ in their chemical composition; however, the correlation of seismic data with the results of petrological high-pressure research has provided evidence for a number of phase boundaries, particularly in the upper mantle. These are due to densification reactions occurring continuously with increasing pressure and lead to new types of compounds and structures in the mantle silicate. At the transition to the metallic core, which consists of an Fe, Si, Ni alloy, the mantle silicates are present in densest atomic packing. While the mantle can be regarded as essentially crystalline, the outer core is liquid. Only in the region of the upper mantle do the temperature and pressure conditions result in a zone of partial melting, manifested on seismic profiles by a reduction in seismic velocities. The causes of magmatism, volcanism, and the tectonic phenomena in the crust should be sought in this zone, the mainspring of all geological activity.

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[1] *H. C. Urey*, Mon. Not. Roy. Astron. Soc. *131*, 199 (1966).
[2] *R. D. Oldham*, Quart. J. Geol. Soc. London *62*, 456 (1906).
[3] *A. Mohorovičić*, Geodis. Izv. Kr. Zem. Zav. Met. Geodin. *9*, 1 (1909).
[4] *H. Jeffreys*, Mon. Not. Roy. Astron. Soc. Geophys. Suppl. *4*, 488, 537, 548, 594 (1939).
[5] *I. Lehmann*, Bur. Centr. Séism. Internat. A. *14*, 3 (1936).
[6] *K. E. Bullen*, Nature *157*, 405 (1946).
[7] *K. E. Bullen*, Mon. Not. Roy. Astron. Soc. *109*, 457, 688 (1949).
[8] *B. Gutenberg*, Trans. Amer. Geophys. Union *32*, 373 (1951).
[9] *B. Gutenberg*, Z. Geophys. *2*, 24 (1926).
[10] *B. Gutenberg* and *C. F. Richter*, Gerlands Beitr. Geophys. *45*, 280 (1935).
[11] *D. L. Anderson*, Science *148*, 3670 (1965).
[12] *T. Jordan* and *D. L. Anderson*, cited in Tectonophysics *4*, 216 (1972).
[13] *C. B. Archambeau, E. A. Flinn*, and *D. G. Lambert*, J. Geophys. Res. *74*, 5825 (1969).
[14] *D. Helmberger* and *R. A. Wiggins*, J. Geophys. Res. *76*, 3229 (1971).
[15] *L. P. Vinnik* and *A. V. Nikolayev*, Izv. Acad. Sci. USSR, Phys. Solid Earth (Transl. of Izv. Akad. Nauk SSSR, Fiz. Zemli) *11*, 24 (1970).
[16] *R. D. Adams* and *M. J. Randall*, Bull. Seismol. Soc. Amer. *54*, 1299 (1964).
[17] *N. Kawai, S. Endo*, and *K. Ito*, Phys. Earth Planet. Interiors *3*, 182 (1970).
[18] *H. B. Wiik*, Geochim. Cosmochim. Acta *9*, 279 (1956).
[19] *A. E. Ringwood*, Geochim. Cosmochim. Acta *20*, 241 (1960).
[20] *A. E. Ringwood* in *P. M. Hurley*: Advances in Earth Science. Contrib. Int. Conf. 1964. M.I.T. Press, Cambridge, Mass. 1966, p. 287, 357.
[21] *H. C. Urey*: The Planets. Yale University Press, New Haven 1952.
[22] *H. C. Urey*, Astrophys. J. *124*, 623 (1956).
[23] *H. C. Urey*, Phys. Chem. Earth *2*, 46 (1957).
[24] *H. C. Urey*, Yearb. Phys. Soc. London *1957*, 14.
[25] *H. C. Urey*, Proc. Chem. Soc. (London) *1958*, 68.
[26] *H. C. Urey*, Geochim. Cosmochim. Acta *26*, 1 (1962).
[27] *H. C. Urey* in *D. P. Le Galley*: Space Science. Wiley, New York 1963, Chap. 4, p. 123.
[28] *D. L. Anderson*, Trans. Amer. Geophys. Union *45*, 101 (1964).
[29] *D. L. Anderson* in *T. F. Gaskell*: The Earth's Mantle. Academic Press, New York 1967, p. 355.
[30] *F. Birch*, Geophys. J. Roy. Astron. Soc. *4*, 295 (1961).
[31] *S. P. Clark* and *A. E. Ringwood*, Rev. Geophys. *2*, 35 (1964).
[32] *D. L. Turcotte* and *E. R. Oxburgh*, J. Geophys. Res. *74*, 1458 (1969).
[33] *H. S. Yoder* and *C. E. Tilley*, J. Petrology *3*, 342 (1962).
[34] *D. H. Green* and *A. E. Ringwood*, Geochim. Cosmochim. Acta *31*, 767 (1967).
[35] *L. L. Fermor*, Geol. Surv. India *43*, Part 1 (1913).
[36] *J. F. Lovering*, Trans. Amer. Geophys. Union *39*, 947 (1958).
[37] *G. C. Kennedy*, Amer. Sci. *47*, 491 (1959).
[38] *F. Press*, J. Geophys. Res. *73*, 5223 (1968); Science *165*, 174 (1969).
[39] *K. Ito* and *G. C. Kennedy* in *B. A. Morgan*: The Fine-Structure of the Basalt-Eclogite Transition. Fiftieth Anniversary Symposia, Min. Soc. of America, Spec. Paper 3 (1970).
[40] *A. E. Ringwood*, J. Geophys. Res. *67*, 857 (1962).
[41] *N. L. Bowen*: The Evolution of the Igneous Rocks. Princeton University Press, Princeton 1928.
[42] *J. Verhoogen*, Trans. Amer. Geophys. Union *35*, 85 (1954).
[43] *J. Verhoogen*, Phys. Chem. Earth *1* (1956).
[44] *H. Kuno, K. Yamasaki, C. Iida*, and *K. Nagashima*, Jap. J. Geol. Geogr., Trans. *28*, 179 (1957).
[45] *A. E. Ringwood* and *D. H. Green*, Tectonophysics *3*, 383 (1966).
[46] *D. H. Green* and *A. E. Ringwood*, J. Geophys. Res. *68*, 937 (1963).
[47] *L. P. Mercy* in *T. F. Gaskell*: The Earth's Mantle. Academic Press, New York 1967, p. 421.
[48] *C. L. Drake* and *J. E. Nafe* in *L. Knopoff, C. L. Durke*, and *P. J. Hart*: The Crust and Upper Mantle of The Pacific Area. Geophys. Monograph 12, Amer. Geophys. Union, Washington 1968.
[49] *A. E. Ringwood*, Phys. Earth Planet. Interiors *3*, 109 (1970).

[50] *B. Bolt, M. O'Neill,* and *A. Qamar*, Geophys. J. Roy. Astron. Soc. *16*, 475 (1968).

[51] *B. Bolt*, cited in Phys. Earth Planet. Interiors *3*, 152 (1970).

[52] *L. Johnson*, Bull. Seismol. Soc. Amer. *59*, 973 (1969).

[53] *K. E. Bullen*, Mon. Not. Roy. Astron. Soc. Geophys. Suppl. *3*, 395 (1936).

[54] *F. Birch*, Bull. Seismol. Soc. Amer. *29*, 463 (1939).

[55] *R. G. McQueen* and *S. P. Marsh* in *S. P. Clark Jr.*: Handbook of Physical Constants. Geol. Soc. Amer. Mem. *1966*, p. 97.

[56] *R. G. McQueen, S. P. Marsh,* and *J. N. Fritz*, J. Geophys. Res. *72*, 4999 (1967).

[57] *W. H. Ramsay*, Mon. Not. Roy. Astron. Soc. *108*, 406 (1948).

[58] *W. H. Ramsay*, Mon. Not. Roy. Astron. Soc. Geophys. Suppl. *5*, 409 (1949).

[59] *F. Birch*, J. Geophys. Res. *57*, 227 (1952).

[60] *L. Knopoff* and *G. J. F. MacDonald*, Geophys. J. Roy. Astron. Soc. *3*, 68 (1960).

[61] *B. Mason*, Nature *211*, 616 (1966).

[62] *A. E. Ringwood*, Geochim. Cosmochim. Acta *25*, 1 (1961).

[63] *D. L. Anderson* and *C. Sammis*, Phys. Earth Planet. Interiors *3*, 41 (1970).

[64] *D. H. Green* and *A. E. Ringwood*, Earth Planet. Sci. Lett. *3*, 151 (1967).

[65] *C. B. Sclar*, Phys. Earth Planet. Interiors *3*, 333 (1970).

[66] *Th. Ernst, G. Mages,* and *R. G. Schwab*, Fortschr. Mineral. *49*, Bh. 1, 91 (1971).

[67] *Th. Ernst* and *R. G. Schwab*, Ref. to DFG-Conference, "Experimentelle Erfahrungen und Fortschritte auf dem Gebiet der Hochdruck-Forschung", Bochum 1972.

[68] *A. Neuhaus*, Geol. Jahrb. Beih. *80*, 57 (1969).

[69] *Th. Ernst* and *R. G. Schwab*, 24th Int. Geol. Congr. 1972, Section 14, p. 28.

[70] *J. Verhoogen*, Phil. Trans. Roy. Soc. London Ser. *A* 1088 (1965).

A Hundred Years of Stereochemistry—The Principal Development Phases in Retrospect

By Jost Weyer[*]

The theory of the arrangement of atoms in space was initiated in 1874 by *van't Hoff* and *Le Bel*. The starting points were mainly in the fields of structural chemistry and optical activity. After early difficulties, stereochemistry gained acceptance in the last quarter of the 19th century and led to many interesting investigations and discoveries: the investigation of geometrical isomerism, the Baeyer strain theory, the stereochemistry of nitrogen, the determination of the configurations of carbohydrates, Walden inversion, and the beginning of inorganic stereochemistry all fall in this period. Theoretical verification of the principal stereochemical hypotheses and the exact determination of the steric arrangement of atoms by physical methods were achieved only in the 20th century.

1. Introduction

A hundred years ago, the foundation stone of stereochemistry was laid by the work of *van't Hoff* and *Le Bel*. In a historical review presented to mark the 25th jubilee of this branch of knowledge[1], *Walden* expressed the view that "there is at present no other theory in modern organic chemistry that is as far-reaching, as rich in problems, and as certain of success as the stereochemical theory". Yet another quarter of a century later, in another review[2a], *Walden* mentioned *Kekulé*'s assertion that most theories do not last longer than 25 years, and expressed surprise that the stereochemical theory was not yet obsolete. Even today, after a hundred years, stereochemistry has lost none of its significance; indeed, during the last 20 years it has undergone an upward swing, whose end is not yet in sight. This is underlined by the award of the 1969 Nobel prize for chemistry to *Barton* and *Hassel*[2b] for their stereochemical work.

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The present article clearly cannot present the entire development of stereochemistry, even in a concise form[3]. From the extensive material available, therefore, I have selected and discussed those facts that in my opinion have contributed decisively to the further development of stereochemistry.

2. The Antecedents of Stereochemistry

Like all scientific ideas, hypotheses, and theories, stereochemistry, as the theory of the arrangement of atoms in space, also has its antecedents. There were three main factors that contributed to the genesis of stereochemistry: the atomic theory, the structural theory of the chemical bond, and optical rotation. Among these factors, only the atomic theory (or some other corpuscular theory) was a necessary condition, since stereochemistry is inconceivable without discrete particles of matter of some kind.

The idea that the particles of matter in a substance have an arrangement in space can be traced back to antiquity, and was mentioned even by the two founders of atomism, *Leucippus* and *Democritus*[4]:

"However, these atoms, which were separated from one another in the infinite void and differed in shape (schema), size (megethos), position (thesis), and arrangement (taxis), moved around in empty space, and on meeting one another they collided; and some bounced apart, as often happens, whereas others became entangled with one another as a result of the symmetry of their shapes, size, position, and arrangement, and remained together; this is how the compound bodies were formed."

This rather vague picture of an arrangement of the atoms in space can be followed throughout the history of atomism, but it was only in the 19th century that it took on a more distinct shape as a result of greatly increased knowledge about the composition of substances.

After *Dalton* had conceived the chemical atomic theory in 1803, *Wollaston* was the first to try and extend *Dalton*'s theory to the arrangement of atoms in space. In a publication from the year 1808, he wrote[5]:

"I am inclined to think, that when our views are sufficiently extended, to enable us to reason with precision concerning the proportions of elementary atoms, we shall find the arithmetical relation alone will not be sufficient to explain their mutual action, and that we shall be obliged to acquire a geometrical conception of their relative arrangement in all three dimensions of solid extension".

For the case of four atoms of one kind combined with one atom of another, according to *Wollaston*'s view, a stable arrangement is achieved "if the four particles are situated at the angles of the four equilateral triangles composing a regular tetrahedron[6]".

In the first half of the 19th century, stereochemical ideas of a general nature were widespread, *i. e.* the chemical compounds were pictured not as an indiscriminate aggregation, but as structured three-dimensional arrangements of atoms. However, few attempts were made to investigate the spatial distribution of the atoms, or at least, as *Wollaston* did, to develop clearer concepts of this distribution; in fact, *Dalton*'s atomic theory itself was doubted by leading investigators, mainly on philosophical grounds.

The development of stereochemical ideas entered a new stage in 1858 when *Couper* and *Kekulé* conceived the valency theory (tetravalency of the carbon atom, linking of atoms to form chains) and this was developed by *Butlerow* into a general structural theory of chemical bonding. Though the bonding of the atoms was the focus of interest in the structural theory, stereochemical ideas also became topical once again, since the bonds were mostly pictured in three dimensions. *Butlerow* in 1862, was the first to apply the tetrahedral model specifically to the carbon atom[7]:

"Nehmen wir ein grobes Beispiel und stellen wir uns das Kohlenstoffatom als ein Tetraëder vor, bei welchem jede der 4 Flächen ein Atom Wasserstoff zu binden im Stande ist, ...[*]."

An innovation introduced as part of the structural theory was the graphic representation of valences with bond lines (represented with dotted lines by *Couper* in 1858 and with continuous lines by *Crum Brown* in 1864), *i. e.* the introduction of structural formulas. To avoid any idea of a planar arrangement of the atoms that might be suggested by structural formulas of this type, and also to assist intuition, some chemists used atomic models made from wood and other materials. As early as 1810, *Dalton* had worked with ball and rod models, and it is known that *Hofmann*, *Baeyer*, and *Kekulé*, among others, used models of this type in the 1860s for teaching purposes. In 1867, *Kekulé* proposed an atomic model for the carbon atom that offered an improvement over earlier models:

"wenn man die vier Verwandtschaftseinheiten des Kohlenstoffs, statt sie in eine Ebene zu legen, in der Richtung hexaedrischer Axen so von der Atomkugel auslaufen lässt, dass sie in Tetraederebnen endigen[8][**]."

Similar atomic models of a wide variety of designs later became an important research instrument for the stereochemist, and have remained so up to the present day.

Optical rotation, which, as was mentioned earlier, contributed along with the atomic theory and the structural theory to the birth of stereochemistry, was discovered in 1811 by *Arago* and investigated further by *Biot*. Optical rotation became interesting in chemistry when *Biot* found that the optical activity is not tied to the crystalline state (as it is in the case of quartz), but that organic substances such as oil of turpentine or solutions of camphor, sucrose, or tartaric acid are also optically active[9].

Biot's work was carried on by *Pasteur*, who investigated the crystalline forms of several salts of tartaric acid and found that all tartrates have hemihedral faces. He therefore assumed that a relationship must exist between the hemihedrism (*i. e.* a crystallographic property) and the optical rotation of the tartrates. This hypothesis was confirmed experimentally in 1848 when *Pasteur*, by manual sorting, succeeded in separating the sodium ammonium salt of optically inactive racemic acid into two crystalline forms that were related to each other as object and mirror image[10]. In aqueous solution, one of these modifications turned the plane of plane-polarized light to the left, and the other to the right. The close connection between crystalline form and rotatory power was thus demonstrated in the case of tartrates. At the same time, *Pasteur*'s discovery was the first example of resolution of a racemate, in this case by spontaneous crystallization. During the next few years he discovered two further resolution methods, *i. e.* the reaction of racemic acid with optically active bases (1852) and biochemical resolution (1858).

In an article summarizing his experiments which was published in 1860, *Pasteur* expressed the following views on the arrangement of the atoms in such compounds[11]:

"Nous savons en effet, d'une part, que les arrangements moléculaires des deux acides tartriques sont dissymétriques, et de l'autre, qu'ils sont rigoureusement les mêmes, avec la seule différence d'offrir des dissymétries de sens opposés. Les atomes de l'acide droit sont-ils groupés suivant les spires d'une hélice dextrorsum, ou placés aux sommets d'un tétraédre irrégulier, ou disposés suivant tel ou tel assemblage dissymétrique déterminé? Nous ne saurions répondre à ces questions. Mais ce qui ne peut être l'objet d'un doute, c'est qu'il y a groupement

[*] "As a crude example, let us imagine the carbon atom as a tetrahedron, each of whose 4 faces is able to bond an atom of hydrogen, ..."

[**] "if the four valences of carbon, instead of lying in a single plane, are allowed to radiate from the atomic sphere in the direction of hexahedral axes so that they terminate in tetrahedral planes".

des atomes suivant un ordre dissymétrique à image non superposable. Ce qui n'est pas moins certain, c'est que les atomes de l'acide gauche réalisent précisément le groupement dissymétrique inverse de celui-ci"[*]."

Pasteur himself was unable to solve this problem but others later followed up his results.

The factor that actually triggered the development of stereochemistry was a number of unexplained cases of isomerism. The first four examples in which substances with the same percentage composition exhibited different chemical behavior were discovered in the 1820's: fulminic acid and cyanic acid, ethylene and butene, ammonium cyanate and urea, tartaric acid and racemic acid. In 1830, *Berzelius* had coined the term isomerism for this phenomenon. Most cases of isomerism were later satisfactorily explained by the structural theory. However, some cases defied all attempts at interpretation; these include the isomerism of maleic and fumaric acid, of the tartaric acids, and of the lactic acids. With regard to the lactic acids, *Wislicenus* said the following in 1869[12]:

"Es ist damit der erste sicher constatirte Fall gegeben, dass die Zahl der Isomeren die Structurmöglichkeiten übersteigen kann. Thatsachen wie diese werden dazu zwingen, die Verschiedenheit isomerer Molecule von gleicher Structurformel durch verschiedene Lagerung ihrer Atome im Raum zu erklären und sich nach bestimmten Vorstellungen darüber umzusehen[**]."

The situation that had arisen was thus one that may be regarded as typical in the history of the natural sciences. *T. S. Kuhn*, who, in his work "The Structure of Scientific Revolutions", has dealt with the development of new fundamental scientific ideas or theories (he himself calls them paradigms)[13], characterizes such a situation as follows: in the "normal" science, which is under a certain paradigm, there first arise anomalies that can no longer be explained by the existing theories. If these anomalies are serious enough, they can trigger a crisis within the scientific community concerned. This crisis is settled only when the facts that were regarded as anomalies in the light of the old paradigm can be satisfactorily explained by a new paradigm. Such a crisis situation in Kuhn's sense existed in organic chemistry at the end of the 1860's, though all chemists did not perceive it as such: The anomalies of the acids mentioned above could no longer be explained under the paradigm of the structural theory. The "revolution"[***] later proved to be an extension of the structural theory.

[*] "We know in fact, on the one hand, that the molecular arrangements of the two tartaric acids are dissymmetric, and on the other that they are exactly the same except that they exhibit dissymmetry in opposite directions. Are the atoms of the right-handed acid grouped in the form of a right-handed spiral, or are they situated at the apices of an irregular tetrahedron, or are they fixed in some dissymmetric arrangement or other? We cannot answer these questions. But there can be no doubt that the atoms are grouped in a dissymmetric arrangement that does not coincide with its mirror image. It is no less certain that the atoms of the left-handed acid have exactly the opposite dissymmetric grouping."

[**] This is thus the first definitely verified case in which the number of isomers can exceed the structural possibilities. Facts such as this will force us to explain the difference between isomeric molecules with the same structural formula by different arrangements of their atoms in space, and to look for definite ideas on these arrangements."

[***] *Van't Hoff* spoke more aptly of a "reform of prevailing views".

3. The Fundamental Stereochemical Work of *van't Hoff* and *Le Bel*

The increasingly frequent need to take into account the arrangement of the atoms in space was satisfied in 1874 by two young chemists: *Joseph Achille Le Bel*, 27 years of age, and *Jacobus Henricus van't Hoff*, 22 years old. These two workers made their discoveries independently of each other, possibly a sign that stereochemical ideas were "in the air" around this time. *Le Bel* had studied at the École Polytechnique, and became an assistant to *Wurtz* at the École de Médicine in Paris. *Van't Hoff* had attended the Polytechnic at Delft and spent a few months with *Kekulé* in Bonn, and, as chance would have it, he also came to *Wurtz* in Paris in the middle of 1873. Though *Le Bel* and *van't Hoff* knew each other, they had at that time, on their own assertion, never discussed stereochemical ideas with each other. In the middle of the following year, *van't Hoff* went to Utrecht to start work for his doctorate. Before he started this work, however, at the beginning of 1874, he issued a 12-page pamphlet in his mother tongue entitled: "Suggestion for the Extension to Three Dimensions of the Structural Formulas Currently used in Chemistry"[14].

In the introduction to his pamphlet, *van't Hoff* stated that the structural formulas used at that time were no longer able to explain certain cases of isomerism, and that this might be due to the absence of ideas about the arrangement of the atoms in space. After the introduction of the tetrahedral model for the carbon atom, he made the following central pronouncement[15]:

"Voor het geval de vier affiniteiten van een koolstof-atoom zijn verzadigd door vier onderling verschillende univalente groepen kunnen twee, en niet meer dan twee verschillende tetraëders worden verkregen, die elkaârs spiegelbeelden zijn, doch nooit zoo gedacht kunnen worden, dat ze elkaâr bedekken, d. i. men heeft the doen met twee isomere structuurformules in de ruimte[*]."

Van't Hoff referred to such an atom as an "asymmetrisch koolstof-atoom". He then showed that any optically active carbon compound contains an asymmetric carbon atom, whereas the converse is not always true. He gave numerous examples from the literature to demonstrate this. *Van't Hoff* also applied the tetrahedral model to the carbon-carbon double bond, two tetrahedra being joined by a common edge. For the case where each of the two doubly bonded carbon atoms carries two different groups, *van't Hoff* predicted another type of isomerism, which is now known as geometrical isomerism. He also gave examples to support this hypothesis.

Two months later, in November 1874, *Le Bel* published his stereochemical conception under the title "Sur les relations qui existent entre les formules atomiques des corps organiques et le pouvoir rotatoire de leurs dissolutions" (The relations that exist between the atomic formulas of organic compounds and the rotatory power of their solutions)[16]. *Le Bel* approached the problem from a different direction from *van't*

[*] "In the case where the four affinities of a carbon atom are saturated by four different univalent groups, it is possible to obtain two and not more than two different tetrahedra, one of which is the mirror image of the other, but which can never be imagined in such a way that they can be brought into coincidence, *i.e.* one has two isomeric structural formulas in space."

Hoff. His hypothesis was based neither on the tetrahedral model of the carbon atom nor on the concept of fixed valences between the atoms. He proceeded from purely geometrical considerations, *i.e.* from symmetry arguments; he spoke of the dissymmetry, not of individual atoms, but of the entire molecule, so that his views would nowadays be classed under the heading of molecular dissymmetry.

Le Bel started with the hypothetical molecule MA_4, where M was an atom or group of atoms joined to four univalent atoms A. If three atoms A are replaced by different substituents, geometric considerations lead to the following rule[17]:

"En général si un corps dérive de notre type primitiv MA^4 par la substitution à A de trois atomes ou radicaux distincts, sa molécule sera dissymétrique et il aura le pouvoir rotatoire[*]."

Le Bel considered that exceptions to this rule were possible. Conversely, if optical activity can be detected for an atom M with four different substituents, then according to *Le Bel* the original groups of atoms A were situated at the apices of a regular tetrahedron. He thus regards the tetrahedral grouping, not as a general principle, but as a special case.

Le Bel then considered substances containing a double bond. Since chemical isomers could be obtained in this case by the introduction of only two different substituents, he assumed that the hydrogen atoms of ethylene, as the simplest substance in this series, were situated at the base corners of a square pyramid. He applied similar symmetry considerations to aromatic and hydroaromatic compounds, and cited numerous examples from the literature to support all his hypotheses.

The roots of the two stereochemical concepts are relatively easy to trace. *Van't Hoff* came from *Kekulé*'s school, *i.e.* from the camp of the structural chemists, and he wished his hypothesis to be understood as an extension of the structural theory to spatial relationships. The tetrahedral atomic models used by *Kekulé* in his lectures presumably also prompted his pupil *van't Hoff*, at least unconsciously, in the conception of the asymmetric carbon atom. *Le Bel*, on the other hand, was trained in the tradition of *Pasteur* (whose investigations he also mentioned expressly in his article), *i.e.* he started out from *Pasteur*'s considerations on the connection between optical rotation and molecular structure.

When *van't Hoff* and *Le Bel* published their hypotheses in 1874, there was nothing new, as is shown by the earlier history, in either general speculations about the arrangement of atoms in space or assumed connections between optical activity and dissymetric molecular structure or the tetrahedral model of the carbon atom. The achievement of *Le Bel* and *van't Hoff* lies rather in the fact that they developed concrete ideas about the three-dimensional arrangement of the singly and doubly bonded carbon atoms, they were able to interpret and predict the occurrence of optical activity and they brought their views into a uniform theoretical system. Both can therefore be justifiably regarded as the founders of stereochemistry.

4. The Reaction of Chemists to the New Hypothesis

Van't Hoff's hypothesis, being more readily appreciable and more specific, came closer to satisfying the immediate needs of chemists; hence the first discussions of the new theory were based not on *Le Bel*'s interpretation but on *van't Hoff*'s. However, even *van't Hoff*'s work was practically ignored at first. To make his ideas known to the scientific world, *van't Hoff* published a French translation of the original work[18], a condensed version[19], and an expanded French version, as a separate pamphlet[20]. He sent copies of this last publication, together with home-made cardboard tetrahedral models, to *Baeyer*, *Butlerow*, *Henry*, *Hofmann*, *Kekulé*, *Frankland*, *Wislicenus*, *Wurtz*, *Berthelot*, and others.

The reaction to these publications was slight. *Wurtz* wrote a letter of agreement, *Baeyer* expressed his approval of the new hypothesis to his pupils, and *Berthelot* politely rejected *van't Hoff*'s views at a meeting of the Société Chimique, while *Kekulé* later, on the occasion of his Bonn rectorial address, gave half-hearted approval to the ideas of his former pupil. However, there was no real discussion such as *van't Hoff* had hoped for. A turning point came when *Wislicenus*, at the end of 1875, asked *van't Hoff* if he might have the French pamphlet translated into German by his assistant *Herrmann*. This translation, which appeared in 1877 with a foreword by *Wislicenus*[21], introduced the phase of scientific discussion.

Kolbe reacted unusually violently[22] after the German translation had been brought to his attention. He attacked not only *van't Hoff* but also *Herrmann* and *Wislicenus*, and he did not even refrain from personal abuse. Among other things he wrote[23]:

"Es ist bezeichnend für die heutige kritikarme und Kritik hassende Zeit, dass zwei so gut wie unbekannte Chemiker, der eine von einer Thierarzneischule, der andere von einem landwirthschaftlichen Institute, die höchsten Probleme der Chemie, welche wohl niemals gelöst werden, speciell die Frage nach der räumlichen Lagerung der Atome, mit einer Sicherheit beurtheilen und deren Beantwortung mit einer Dreistigkeit unternehmen, welche den wirklichen Naturforscher geradezu in Staunen setzt[*]."

Irrelevant and defamatory as this criticism was, it nevertheless made a decisive contribution to the dissemination of *van't Hoff*'s views.

In retrospect, one might ask why the stereochemical ideas met with so much indifference and rejection. An only apparently trivial answer is found if the scientists in question are grouped according to their age: *Wislicenus*, *Landolt*, *E. Fischer*, *Wallach*, *Baeyer*, *V. Meyer*, *Auwers*, *Werner*, and *Hantzsch* were all between twenty and fifty years of age when they started their stereochemical work, *i.e.* they belonged to the younger generation (not forgetting *Le Bel* and *van't Hoff* themselves). On the other hand, the advocates of classical organic chemistry, *e.g. Butlerow*, *Kekulé*, *Hofmann*, *Beilstein*, *Pasteur*, *Dumas*, and *Wurtz*, all of whom except *Beilstein* were roughly fifty years of age or older, showed little interest in the expansion of the structural theory toward three-dimensional views. This is thus a case of the validity of *Planck*'s assertion that a new scientific truth usually becomes accepted, not because

[*] "If a substance is derived from our original type MA_4 by substitution of A by three different atoms or radicals, its molecule will generally be dissymmetric and possess rotatory power."

[*] "It is typical of the present time, when there is so little criticism and so much hatred of criticism, that two practically unknown chemists, one from a veterinary college and the other from an agricultural institute, pass judgment on the loftiest problems of chemistry, which will probably never be solved, particularly the question of the position of atoms in space, with an assurance, and undertake to answer these problems with an impudence, that absolutely astonish the true scientist."

its opponents have been convinced, but because the opponents gradually die out and the rising generation has been made familiar with it from the outset[24].

However, there is also a more profound reason for the rejection of stereochemistry by the older generation of chemists. Influenced by the philosophy of *Auguste Comte*, many chemists believed that it was fundamentally impossible to determine the actual structure of compounds. Thus *Berthelot* and *Kolbe* had already rejected the structural theory, and even the type theory. Even *Kekulé*, one of the founders of the structural theory, was doubtful about the reality presented by structural formulas. In his opinion, these were merely reaction formulas and could in no way express the actual arrangement of the atoms in a compound. *Kolbe* repeatedly expressed the view that it would never be possible to determine the arrangement of atoms in space. When two young, inexperienced chemists now believed that they had solved these "loftiest problems of chemistry", this appeared to *Kolbe* as a dangerous reversion to speculative *Naturphilosophie*.

5. The Development of Classical Stereochemistry

After the first, in part philosophically grounded reactions to the stereochemical ideas had died down, stereochemistry entered a phase of objective discussions based on experimental arguments. The chemists had a new paradigm in *Kuhn*'s sense: The problem was to verify or refute the theoretically predicted relationships between the arrangement of atoms in space and optical activity (*e. g.* the number of isomers for a given number of asymmetric carbon atoms). One of the principal pieces of evidence was the resolution of optically inactive compounds containing asymmetric carbon atoms into their optical antipodes, for which *Pasteur* had already developed the methods. In all these investigations, the Le Bel-van't Hoff hypothesis was confirmed time and again, and apparent anomalies later proved to be incorrect interpretations.

The turning point came in the middle of the 1880's, when a number of important chemists incorporated stereochemical questions into their research program: in addition to *Wislicenus*, mainly *Baeyer*, *E. Fischer*, and *V. Meyer* in Germany and *Le Bel* in France. During the first few decades there emerged regular schools of stereochemists, most of whom can be traced back to *Wislicenus* or *Kekulé*. Thus *Werner* was a pupil of *Hantzsch*, who in turn was a pupil of *Wislicenus*; *Fischer* was a pupil of *Baeyer*, and the latter was a pupil of *Kekulé*.

The interest in stereochemistry can also be seen from the numerous editions and translations of *van't Hoff*'s "Lagerung der Atome im Raume" (Arrangement of Atoms in Space)[*] and from the appearance of the first textbooks and handbooks of stereochemistry[3d, 25, 26]. Stereochemistry was also introduced into chemical textbooks. The growth of stereochemistry can be traced out quantitatively too: Whereas 20 optically active compounds were known in 1874, the number in 1904 was more than 900; *van't Hoff*'s Dutch pamphlet covered 12 pages, while *Freudenberg*'s handbook covered 1500. The necessary terminology was also created: in 1880 *V. Meyer* coined the expressions stereochemistry and stereochemical and in 1886 *Wunderlich* proposed the term configuration (stereochemical) as distinct from constitution (structure-chemical).

Of the numerous stereochemical investigations that were started in the last quarter of the 19th century, only a few of the most important can be mentioned here. These include *Baeyer*'s strain theory, which was conceived in 1885 by *Adolf Baeyer*[27], to explain the difference in the ring-forming tendencies of cyclic compounds and the reactivity of compounds containing double or triple bonds. *Baeyer* extended the van't Hoff-Le Bel hypothesis by the assumption that deviations from the tetrahedral angle are possible and that these would lead to "strain" in the bonds. The greater the "distortion" of the tetrahedral angle, the greater the strain should be. On the basis of the model, *Baeyer* calculated the deviations from the ideal tetrahedral angle for carbocyclic systems from cyclopropane to cyclohexane, starting with the tacit assumption that all these rings are planar. He also included the double bond in his considerations by regarding it as a two-membered ring. He came to the conclusion that the five-membered ring should be formed most easily, since the deviation from the tetrahedral angle is least in this case, and that the strain should increase with decreasing and with increasing ring size. Considerable limitation of *Baeyer*'s original strain theory was later found to be necessary, but it proved at the time to be a very fruitful hypothesis.

Whereas the views of *Le Bel* and *van't Hoff* on the stereochemistry of singly bonded carbon became accepted relatively quickly after the early resistance, it took longer for their hypotheses on the steric arrangement of compounds containing carbon-carbon double bonds to gain acceptance. The body of facts available was still small, so that it was still possible to hope that one of the traditional explanations might suffice. The break-through in this area was due to *Johannes Wislicenus*, who investigated the steric relationships in double-bond systems in an extensive study planned on a broad experimental basis[28], and coined the term "geometrical isomerism" for the cases of isomerism found in this study. A new and highly successful feature was the idea that one could often decide, on the basis of the reaction behavior, which of the possible isomers is present or which configuration is favored.

The extension of the tetrahedral model to ring and double-bond systems was associated with a conceptual obstacle. In these two cases one either assumed angled or bent bonds, in which case the bond was no longer the straight line between the centers of two atoms, or else two bonds of the carbon were bent into parallel positions, and one could then no longer speak of a tetrahedron. However, most chemists were not fully aware of this contradiction, and this relativization of the tetrahedral postulate was accepted without rejection of the model as such[29].

A decisive test of the new theory was provided by *Emil Fischer*'s carbohydrate syntheses[30]. In an extensive systematic study, *Fischer* was able to determine the relative configurations of numerous sugars and their relations to one another, and in no single case did he find any contradiction of the predictions of the Le Bel-van't Hoff theory. The foundation stone was thus laid for the countless determinations of the configurations of natural products that are today still a subject of investigation

[*] The German translation appeared in several editions and revisions (1892, 1894, 1908, as also did the French version (1887, 1892). The work was also translated into English (1891, 1898, 1901) and Russian (1911).

by organic chemists. *Fischer*'s work was also important in another respect. He introduced a new two-dimensional notation for the characterization of the relative configurations of optically active compounds; as his reference substance he first chose saccharic acid[31], then tartaric acid[32], and this was later replaced by glyceraldehyde[33]. *Fischer*'s notation for asymmetric carbon atoms, which proved to be valuable in particular for carbohydrates and amino acids, was recently modified by the *R,S* notation of configurations in such a way that it is possible to characterize all classes of substances[34].

There was no immediate need for a stereochemistry of nitrogen until the end of the 1880's, when a number of cases of isomerism were discovered in the oximes, for which the usual structural formulas were no longer adequate. A satisfactory explanation of the number of isomers observed was achieved by *Alfred Werner* and *Arthur Hantzsch* in an article published in 1890[35], which became the foundation of the stereochemistry of trivalent, double-bonded nitrogen. These authors also started with the van't Hoff-Le Bel hypothesis, which they extended by the following assumption[36]:

"Die drei Valenzen des Stickstoffatomes sind bei gewissen Verbindungen nach den Ecken eines (jedenfalls nicht regulären) Tetraëders hin gerichtet, dessen vierte Ecke vom Stickstoffatom selbst eingenommen wird[*]."

Van't Hoff had tried to explain the C—C double bond by two tetrahedra joined by one edge. *Werner* and *Hantzsch* now placed the nitrogen atom and the substituent bonded to the nitrogen at the two free apices of one of the tetrahedra, and they used this to describe the geometric relationships of the C—N double bond. By repeating the process in the second tetrahedron, they obtained the steric arrangement of the N—N double bond. Though the tetrahedral model suffered some rather hard wear here, the analogy with geometrical isomerism of the ethylene type proved to be apt, and *Hantzsch* and *Werner* were able to predict correctly the number of possible isomers and in some cases even the presence of one of the possible forms.

During the 1890's, there were numerous hypotheses regarding the stereochemistry of pentavalent nitrogen, but little experimental material was available. Conclusive proof of the optical activity of asymmetric nitrogen was obtained only in 1899, when independent experiments by *Le Bel*[37] and by *Pope* and *Peachey*[38] resulted in the resolution of quaternary ammonium compounds with four different substituents into their optical antipodes. *Pope* later also prepared optically active compounds of sulfur, selenium, and tin.

Whereas steric considerations had at first been confined to carbon and nitrogen, *Werner* expanded them into a stereochemistry of the chemical elements in general. He laid the foundation stone in 1893 in a classical study, in which he also founded the discipline of coordination chemistry[39]. For cobalt complexes with six ligands he proposed the form of an octahedron, and for platinum complexes with four ligands a square arrangement, the metal atom in each case being situated in the center of the system. With the aid of these steric ideas he was able to explain the number of isomers observed for coordination compounds. In the course of his further investigations, which were carried out mainly in the first decade of the 20th century, *Werner* demonstrated geometrical isomerism and mirror-image isomerism in complexes of cobalt, chromium, platinum, and other metals, discovered cases of optical activity without any asymmetric central atom (confirming *Le Bel*'s views on molecular asymmetry), and proved his hypotheses by the resolution of complex compounds into their optical antipodes.

6. Stereochemistry and Mechanism of Chemical Reactions

Around the turn of the century, there was still a long way to go for a stereochemistry of chemical reactions, but two chance discoveries made in the 1890's steered chemical research in this direction; these discoveries were "steric hindrance" and "Walden inversion".

Victor Meyer found that only very low yields could be achieved in the esterification of mesitylenecarboxylic acid, triphenylacetic acid, and similar compounds. These observations led him to the idea that the hindrance of such reactions was caused mainly by the bulk of neighboring substituents[40], and he therefore called this phenomenon "steric hindrance of chemical reactions".

In 1896, *Paul Walden* discovered an "optical cycle", which led from levorotatory malic acid *via* dextrorotatory chlorosuccinic acid, dextrorotatory malic acid, and levorotatory chlorosuccinic acid back to the starting material[41]. Since two pairs of optical antipodes had been produced in this process, inversion of the configuration on the asymmetric carbon atom must have occurred at two points in the cycle. *Walden*'s discovery, which was soon found to be a widely occurring phenomenon, led to the question of the stability of the four groups bonded to the asymmetric carbon atom and the mechanism of substitution processes. At the same time it raised serious doubts as to the reliability of the determination of configurations in which substitutions on the asymmetric carbon atom had been carried out.

Numerous hypotheses were proposed to explain the Walden inversion, but it was not until forty years later that *Hughes* and *Ingold* found a satisfactory explanation, which also allowed predictions for the first time[42]. On the basis of their extensive studies on the mechanism of substitution reactions, these authors found that Walden inversion generally occurs in bimolecular substitutions (S_N2 and S_E2) on the asymmetric carbon. These substitutions proceed *via* a transition state in which the entering substituent is on one side of the carbon atom, and the original substituent on the other; as the original substituent leaves, the configuration "flips over".

7. Hindered Rotation about Single Bonds and Conformation

In 1877, *van't Hoff* had expressed the supposition that rotation must be possible about the carbon-carbon single bond[43].

[*] "The three valences of the nitrogen atom are directed in certain compounds toward the apices of an (irregular) tetrahedron, whose fourth apex is occupied by the nitrogen atom itself."

Though this view was doubted in some cases, it was found that the experimental results could also be interpreted without the assumption of hindered rotation.

The first considerations of conformation[*] in the narrower sense that did not prove to be incorrect interpretations were concerned with the cyclohexane system. On the basis of model considerations and purely mathematical calculations, *Sachse* found in 1890 that *Baeyer*'s strain theory was invalid for six-membered and higher rings, and that strain-free rings could be constructed with retention of the tetrahedral angle[44]. For cyclohexane he established two forms, which are now known as the chair and boat conformations. *Sachse*'s views were not accepted by his contemporaries, partly because they were unable to prevail against the strain theory of the famous *Baeyer*, and partly because *Sachse* considered the isolation of the two forms as conceivable. Almost thirty years later, *Mohr* adopted *Sachse*'s hypothesis[45] and showed that it has unlimited validity for cyclohexane if one assumes that there is only a low energy barrier between the two forms. He extended *Sachse*'s views to bicyclic and polycyclic six-membered ring systems and to diamond. *Mohr*'s prediction that decalin should have strain-free *cis* and *trans* forms was confirmed experimentally by *W. Hückel*, who isolated the two forms[46]. Similarly, the work of *Böeseken* on the boric acid and isopropylidene derivatives of cyclic diols contributed to the ultimate acceptance of the Sache-Mohr theory[47].

Incentives to conformational considerations were also coming in the meantime from another quarter. In 1922, *Christie* and *Kenner* resolved 4,6-dinitrodiphenic acid and 4,4',6,6'-tetranitrodiphenic acid into their optical antipodes[48]. One of the suggested explanations, *i.e.* that rotation about the common axis is prevented here by the bulk of the *ortho* substituents, with the result that the two benzene rings do not lie in the same plane (later known as atropisomerism), soon proved to be correct. Even ethane, which had previously been regarded as the prototype of a molecule with free rotation, was found to exhibit hindrance of the rotation. *Kemp* and *Pitzer* found, by comparison of calculated and experimental entropy values, that an energy barrier of about 3 kcal/mol must be assumed for the rotation of the methyl groups in ethane[49].

Despite the hindrance of rotation observed in these cases, considerations of conformation were at that time still of minor importance to the organic chemist, since there were practically no experimental aids for the detection of conformational effects. This situation was changed by the physico-chemical investigations carried out in the 30's and 40's by research groups working with *Mizushima*[50], *Hassel*[51], and *Pitzer*[52]. Special mention should be made of an investigation by *Hassel*, in which he showed by electron diffraction experiments on simple cyclohexane derivatives that these are nearly always in the chair form, that it is possible to distinguish between axial and equatorial substituents, and that the chair form with the greater number of equatorial substituents is the more stable[51a].

However, the actual flowering period of conformational analysis did not begin until 1950, when *Barton* showed, in a fundamental study on the conformations of steroids, that important conclusions regarding the stability and reaction behavior of chemical compounds can be drawn from considerations of conformation[53]. The rapid acceptance of conformational ideas in organic chemistry that now began was favored by the improvements in X-ray structural analysis and NMR spectroscopy during the 50's and 60's, as a result of which it was possible for many conformation determinations to be carried out.

[*] The term "conformation" was coined by *Haworth* in 1929.

8. Theoretical and Experimental Confirmation of the Fundamental Stereochemical Postulates

The van't Hoff-Le Bel hypotheses and their extensions, *e.g.* by *Baeyer*'s strain theory, raised a number of questions regarding the nature of the valence and the structure of the atoms. For example, the physical reality underlying the tetrahedral model and the postulate of free rotation around single bonds and a rigid arrangement around double bonds was unknown. It was also uncertain whether the steric phenomena were due to intrinsic properties of the atom and whether directed valences actually existed. Such problems could at first only be treated on a purely speculative basis.

Opinions were divided in particular on the question of directed valences. *Van't Hoff* was of the view that the number and direction of the valences must be connected with the shape of the atoms[54]. *Wislicenus* regarded the atoms as three-dimensional forms with preferred valence sites[55]. He thought it conceivable that the carbon atom was at least approximately tetrahedral in shape, and that the sites of action of the valences were concentrated at the apices of the tetrahedron.

Le Bel belonged to the group that rejected the idea of valences fixed in space[56]. In his view, the fixed position of the atoms in space resulted from an interplay between the spheres of attraction and repulsion of the atoms, a state of equilibrium being reached with a certain steric arrangement. *Werner* too was opposed to directed individual valences, since he regarded the affinity as a force acting uniformly in all directions from the center of the atom[57]. Like *Le Bel*, *Werner* therefore considered the tetrahedral arrangement of the substituents around a carbon atom as a secondary effect, which, in the case of four identical substituents, results purely from the fact that this is how the greatest bond strength can be achieved.

A theoretical interpretation of the main stereochemical postulates that was satisfactory to the chemist was made possible only by the quantum theory. The decisive contribution to the solution of the problem is found in an article published in 1931 by *Linus Pauling*, which provided the foundation for the quantum-mechanical interpretation of the chemical bond[58]. Among other things, *Pauling* calculated the eigenfunctions for an sp^3-hybridized atom and summarized his findings as follows[59]:

"We have thus derived the result that an atom in which only s and p eigenfunctions contribute to bond formation and in which the quantization in polar coordinates is broken can form one, two, three, or four equivalent bonds, which are directed toward the corners of a regular tetrahedron. This calculation provides the quantum mechanical justification of the chemist's tetrahedral carbon atom."

Since the arrangement of these eigenfunctions is cylindrically symmetrical with respect to the direction of the bond, *Pauling*

concluded that there must be free rotation about a single bond, provided that the rotation is not hindered by steric effects.

For the double bond, *Pauling* in the same article and *E. Hückel*[60] independently came to the conclusion that maximum overlap of the eigenfunctions is possible only in two arrangements of the substituents in relation to the double bond, these arrangements differing from each other by 180° (*cis* and *trans* arrangements), and that free rotation is lost in double-bond systems. Thus the fundamental hypotheses of stereochemistry, which chemists had already been using for decades, were now provided with a theoretical foundation.

Experimental proof of *van't Hoff*'s tetrahedral model had become possible after the two *Braggs* had determined the crystal structure of diamond by X-ray structural analysis[61]. *Mohr* proposed two models based on carbon tetrahedra for diamond, and showed that one of these models is identical with the Bragg space lattice[45]. These results were confirmed *inter alia* by *Astbury*, who determined the crystal structure of dextrorotatory tartaric acid[62].

One problem that remained unsolved, even after *Astbury*'s investigations, was the determination of the absolute configuration, *i.e.* the question of the actual arrangement in space of the substituents on an asymmetric carbon atom. This problem was clarified only in 1951, *i.e.* more than 75 years after the fundamental hypotheses of *van't Hoff* and *Le Bel*, when *Bijvoet* determined the absolute configuration of sodium rubidium (+)-tartrate by X-ray structural analysis[63]. It was found that the configuration arbitrarily assigned by *Fischer* to dextrorotatory tartaric acid[32] corresponds to the true arrangement in space.

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Translated by Express Translation Service, London

[1] *P. Walden*, Naturwiss. Rundsch. *15*, 145, 157, 169, 185, 197 (1900).

[2a] *P. Walden*, Ber. Deut. Chem. Ges. *58*, 237 (1925); Naturwissenschaften *13*, 301, 331, 352, 376 (1925).

[2b] *D. H. R. Barton*, Angew. Chem. *82*, 827 (1970); *O. Hassel*, *ibid.* *82*, 821 (1970).

[3] Detailed information on the history of stereochemistry can be found in the articles cited under [1] and [2a] and in the following works: a) *E. Hjelt*: Geschichte der Organischen Chemie von ältester Zeit bis zur Gegenwart. Vieweg, Braunschweig 1916; b) *C. Graebe*: Geschichte der organischen Chemie. Springer, Berlin 1920, reprint 1972; c) *P. Walden*: Geschichte der organischen Chemie seit 1880. Springer, Berlin 1941, reprint 1972; d) *C. A. Bischoff* and *P. Walden*: Handbuch der Stereochemie. Bechhold, Frankfurt a. M. 1894; e) *G. W. Bykow*: Istorija stereochimii organičeskikh soedinenij [History of the stereochemistry of organic compounds]. Nauka, Moscow 1966 (regrettably available only in Russian at present). All the books and articles mentioned here were taken as secondary sources.

[4] *Simplicius*: Kommentar zu Aristoteles, Vom Himmel, 242, 15 (Leukipp-Fragment 67 A 14). In: *H. Diels* and *W. Kranz*: Die Fragmente der Vorsokratiker, Vol. 2, 16th Edit., Weidmann, Dublin–Zürich 1972, p. 75.

[5] *W. H. Wollaston*, Phil. Trans. Roy. Soc. London *98*, 96 (1808). See p. 101.

[6] Cf. [5], p. 102.

[7] *A. Butlerow*, Z. Chem. *5*, 297 (1862). See p. 299.

[8] *A. Kekulé*, Z. Chem. [2] *3*, 214 (1867). See p. 218.

[9] *J. B. Biot*, Mém. Acad. Sci. Inst. Fr. *2*, 41 (1817); *13*, 39 (1835).

[10] *L. Pasteur*, Ann. Chim. Phys. [3] *24*, 442 (1848).

[11] *L. Pasteur*: Recherches sur la dissymétrie moléculaire des produits organiques naturels. Paris 1861. Reprinted in: Œuvres de Pasteur, Vol. 1, Masson, Paris 1922, pp. 314–344. See p. 327.

[12] *O. Meister*, Ber. Deut. Chem. Ges. *2*, 619 (1869). See p. 620.

[13] *T. S. Kuhn*: The Structure of Scientific Revolutions. University of Chicago Press, Chicago 1962.—2nd Edit. 1970.

[14] *J. H. van't Hoff*: Voorstel tot uitbreiding der tegenwoordig in de scheikunde gebruikte structuur-formules in de ruimte. Greven, Utrecht 1874.

[15] Cf. [14], p. 4.

[16] *J. A. Le Bel*, Bull. Soc. Chim. Paris [2] *22*, 337 (1874).

[17] Cf. [16], p. 338.

[18] *J. H. van't Hoff*, Arch. Néer. Sci. Exactes Natur. *9*, 445 (1874).

[19] *J. H. van't Hoff*, Bull. Soc. Chim. Paris [2] *23*, 295 (1875).

[20] *J. H. van't Hoff*: La chimie dans l'espace. Bazendijk, Rotterdam 1875.

[21] *J. H. van't Hoff*: Die Lagerung der Atome im Raume. Vieweg, Braunschweig 1877.

[22] *H. Kolbe*, J. Prakt. Chem. [2] *15*, 474 (1877).

[23] Cf. [22], p. 475.

[24] *M. Planck*, Naturwissenschaften *33*, 230 (1946). See p. 235.

[25] *A. Werner*: Lehrbuch der Stereochemie. Fischer, Jena 1904.

[26] *K. Freudenberg*: Stereochemie – Eine Zusammenfassung der Ergebnisse, Grundlagen und Probleme. Deuticke, Leipzig–Wien 1933.

[27] *A. Baeyer*, Ber. Deut. Chem. Ges. *18*, 2269 (1885).

[28] *J. Wislicenus*, Abh. Math.-Phys. Kl. Königl. Sächs. Ges. Wiss. *14*, 1 (1887).

[29] *H. Weissbach*: Strukturdenken in der organischen Chemie. VEB Deutscher Verlag der Wissenschaften, Berlin 1971, p. 79.

[30] *E. Fischer*, Ber. Deut. Chem. Ges. *23*, 2114 (1890); *24*, 1836, 2683 (1891); *27*, 3189 (1894).

[31] *E. Fischer*, Ber. Deut. Chem. Ges. *24*, 2683 (1891).

[32] *E. Fischer*, Ber. Deut. Chem. Ges. *29*, 1377 (1896).

[33] *A. Wohl* and *F. Momber*, Ber. Deut. Chem. Ges. *50*, 455 (1917).

[34] *R. S. Cahn* and *C. K. Ingold*, J. Chem. Soc. *1951*, 612; *R. S. Cahn*, *C. K. Ingold*, and *V. Prelog*, Experientia *12*, 81 (1956); Angew. Chem. *78*, 413 (1966); Angew. Chem. internat. Edit. *5*, 385 (1966).

[35] *A. Hantzsch* and *A. Werner*, Ber. Deut. Chem. Ges. *23*, 11 (1890).

[36] Cf. [35], p. 18.

[37] *J. A. Le Bel*, C. R. Acad. Sci. *129*, 548 (1899).

[38] *W. J. Pope* and *S. J. Peachey*, J. Chem. Soc. *1899*, 1127.

[39] *A. Werner*, Z. Anorg. Chem. *3*, 267 (1893).

[40] *J. van Loon* and *V. Meyer*, Ber. Deut. Chem. Ges. *29*, 839 (1896).

[41] *P. Walden*, Ber. Deut. Chem. Ges. *29*, 133 (1896).

[42] *E. D. Hughes* and *C. K. Ingold*, J. Chem. Soc. *1935*, 244.

[43] Cf. [21], p. 6.

[44] *H. Sachse*, Ber. Deut. Chem. Ges. *23*, 1363 (1890); Z. Phys. Chem. *10*, 203 (1892).

[45] *F. Mohr*, J. Prakt. Chem. [2] *98*, 315 (1918).

[46] *W. Hückel*, Liebigs Ann. Chem. *441*, 1 (1925).

[47] *J. Böeseken*, Rec. Trav. Chim. Pays-Bas *40*, 553 (1921).

[48] *G. H. Christie* and *J. Kenner*, J. Chem. Soc. *1922*, 614.

[49] *J. D. Kemp* and *K. S. Pitzer*, J. Chem. Phys. *4*, 749 (1936).

[50] *S. Mizushima* and *K. Higasi*, J. Chem. Soc. Jap. *54*, 226 (1933); *S. Mizushima*: Structure of Molecules and Internal Rotation. Academic Press, New York 1954.

[51] *O. Hassel*, a) Tidsskr. Kjemi Bergv. Met. *3*, 32 (1943); b) Quart. Rev. Chem. Soc. *7*, 221 (1953).

[52] *C. W. Beckett*, *K. S. Pitzer*, and *R. Spitzer*, J. Amer. Chem. Soc. *69*, 2488 (1947).

[53] *D. H. R. Barton*, Experientia *6*, 316 (1950).

[54] *J. H. van't Hoff*: Ansichten über die organische Chemie. Part 1. Vieweg, Braunschweig 1878, p. 3.

[55] *J. Wislicenus*, Ber. Deut. Chem. Ges. *21*, 581 (1888).

[56] *J. A. Le Bel*, Bull. Soc. Chim. Paris [3] *3*, 788 (1890).

[57] *A. Werner*, Vierteljahresschr. Naturforsch. Ges. Zürich *36*, 129 (1891).

[58] *L. Pauling*, J. Amer. Chem. Soc. *53*, 1367 (1931).

[59] Cf. [58], p. 1378.

[60] *E. Hückel*, Z. Elektrochem. Angew. Phys. Chem. *36*, 641 (1930); Z. Phys. *60*, 423 (1930).

[61] *W. H. Bragg* and *W. L. Bragg*, Proc. Roy. Soc. (London) *A 89*, 277 (1913).

[62] *W. T. Astbury*, Proc. Roy. Soc. (London) *A 102*, 506 (1923).

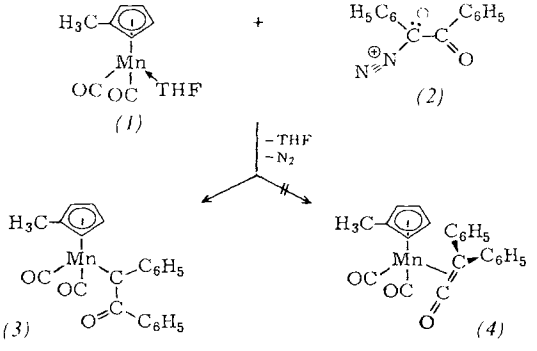
[63] *J. M. Bijvoet*, *A. F. Peerdeman*, and *A. J. van Bommel*, Nature *168*, 271 (1951).

A New Method for the Preparation of Transition Metal-Carbene Complexes

By *Wolfgang Anton Herrmann*[*]

As a rule the Wolff rearrangement of diazoketones[1] proceeds so rapidly that mostly only the corresponding ketene can be isolated in which intramolecular rearrangement has completely terminated. Only under narrowly defined conditions can the intermediary ketocarbene be intercepted by an intermolecular reaction[2]. Heavy-metal ions, such as Ag^+ or Cu^{2+} have proven effective as stabilizers of the reactive carbenes[3].

Reaction of dicarbonyl(η-methylcyclopentadienyl)(tetrahydrofuran)manganese *(1)* with an excess of α-diazodeoxybenzoin *(2)* in tetrahydrofuran (THF) leads to slow evolution of nitrogen and formation of a brownish-black crude product, which on separation by column chromatography yields an emerald-green crystalline compound that is stable to air and deflagrates when heated in a sealed tube at 90.5 °C. Molecular weight determination and elemental analysis show the new compound to have the composition $C_{22}H_{17}O_3Mn$; physical data and spectroscopic findings prove it to have the structure of a benzoylphenylcarbene complex *(3)* and at the same time rule out formation of the isomeric diphenylketene complex *(4)*[4].



Complex *(3)*, which is readily soluble in polar and apolar organic solvents, shows a strong absorption band in the visible region of the spectrum ($\lambda = 387$ nm; $\varepsilon = 12800$ l/mol·cm) while *(4)* absorbs only below 250 nm.—The IR spectrum of *(3)* exhibits two strong, almost equally intense bands in the stretching region of the terminal carbonyl groups bound to the metal atom (1979 and 1920 cm^{-1}, diethyl ether). The $\nu_{C=O}$ frequency of the benzoyl group of the carbene ligand occurs at 1628 cm^{-1} (KBr; *(2)*: 1631 cm^{-1}).—The ^{1}H-NMR spectrum contains two highly structured multiplets at $\tau \approx 2.4$ and 2.6 ppm which are assigned to the two C_6H_5 groups. The spin system of the C_5H_4-protons likewise appears as a multiplet at $\tau = 5.1$ ppm, and the CH_3 singlet occurs at $\tau = 8.19$ ppm. In the decomposition of *(3)* in the mass spectrometer (70 eV) the two CO groups bound to the central metal are eliminated first; the molecular ion of tolan ($m/e = 178$), which is formed by deoxygenation of the carbene ligand, is also observed.

Dicarbonyl(η-methylcyclopentadienyl)(benzoylphenylcarbene)-manganese (3):

A 1 M solution (8 ml, 8 mmol) of α-diazodeoxybenzoin *(2)*[5] in benzene is added dropwise to a stirred solution of the THF-complex *(1)*—which is formed photochemically from $(CH_3C_5H_4)Mn(CO)_3$ (1.09 g, 5 mmol)—in THF (30 ml). The mixture is stirred for 48 h at room temperature, concentrated in a water-jet vacuum, and the resulting oily, brownish-black residue is then degassed for 5 h in a high vacuum. On chromatographic separation on a silica gel column ($l = 45$, $\varnothing = 2.5$ cm) with benzene the first yellow zone consists of a mixture of $(CH_3C_5H_4)Mn(CO)_3$ and diphenylketene. This is followed by a very short blue zone, which so far has not been characterized. The carbene complex *(3)* is contained in the third brown zone. The eluate is concentrated and the resulting viscous oil is dried in a high vacuum prior to dissolution in the minimum amount of *n*-pentane/diethyl ether (3 : 1). On cooling the brown solution, emerald green *(3)* crystallizes out at −50 °C [yield: 710 mg (37 %)].

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[1] *L. Wolff*, Liebigs Ann. Chem. *325*, 144 (1902).

[2] *B. Eistert, M. Regitz, G. Heck*, and *H. Schwall* in: Methoden der organischen Chemie (Houben-Weyl), 4. Edit., Vol. X/4, p. 855ff. Thieme-Verlag, Stuttgart 1968.

[3] *R. Huisgen, H. König, G. Binsch*, and *H. J. Sturm*, Angew. Chem. *73*, 368 (1961); and literature cited therein.

[4] *W. A. Herrmann*, Angew. Chem. *86*, 345 (1974); Angew. Chem. internat. Edit. *13*, 335 (1974).

[5] Synthesis: *H. Staudinger*, Ber. Deut. Chem. Ges. *49*, 1911 (1916).

Modes of Reaction of 2- and 3-Hydroxyalkyl Isocyanides with Metal Compounds; Oxazolidinylidene and Perhydrooxazinylidene Complexes of Palladium, Platinum, and Gold[**]

By *Klaus Bartel* and *Wolf Peter Fehlhammer*[*]

Isocyanides are generally stabilized when coordinated to a metallic center. We have found, however, that isocyanides with OH groups at position 2 or 3, which are stable as pure substances, become activated on contact with metal ions and isomerize to *N,O*-heterocycles.

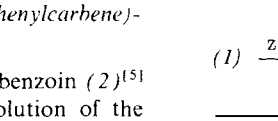
2-Hydroxyethyl isocyanide *(1)* [b. p. 54—55.5 C/10^{-3} torr] and 3-hydroxypropyl isocyanide *(2)* [b. p. 48—50 C/10^{-3} torr] are readily accessible from the corresponding formamides using phosgene as dehydrating agent, according to eq. (1). With an excess of phosgene the crystalline bis(isocyanoalkyl) carbonates are formed[1].

$$HO\text{–}(CH_2)_n\text{–}NHCHO + COCl_2 + 2\ NEt_3 \rightarrow$$

$$HO\text{–}(CH_2)_n\text{–}NC + CO_2 + 2\ [Et_3NH]Cl \qquad (1)$$

(1), n = 2
(2), n = 3

If even a few grains of $ZnSO_4$ or $PdCl_2$ are added to *(1)*, a vigorous exothermic reaction sets in, leading quantitatively to 2-oxazoline *(3)*.



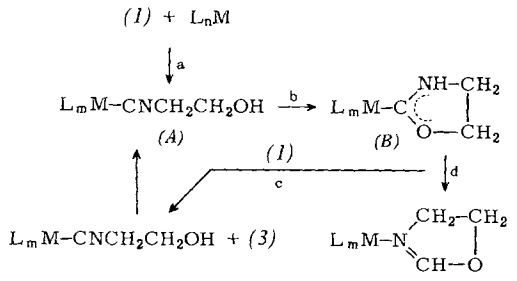
(2)

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[**] Metal Complexes with Multifunctional Isocyanides, Part 1. This work was supported by the Deutsche Forschungsgemeinschaft.

Complete catalytic cyclization of *(2)* to 5,6-dihydro-4*H*-1,3-oxazine requires warming for several days at 60 °C[2].

The reaction scheme shown in eq. (3) for catalytic isomerization of *(1)* is supported by the isolation and characterization of the isocyanide *(A)* and carbene intermediates *(B)*.

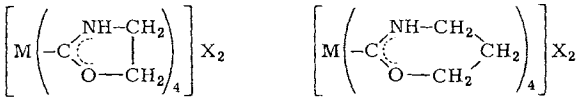


(3)

L_nM = PdI_2, $(C_6H_5CN)_2PdCl_2$, *(4c)*, $PtCl_2$, $AuCl_4^-$, Zn^{2+}

With a stoichiometric ratio of L_nM to isocyanide and suitable metal-complex components L_nM, the reaction can be arrested at stage *(A)* or *(B)*, but this is not possible with catalytic amounts of metal salts because of the substitution step c. In the reaction of the carbonyl compounds $M(CO)_5THF$ or $C_7H_8Mo(CO)_3$ with *(1)* or *(2)* the stable "open-chain" isocyanide complexes of the type corresponding to formula *(A)*, namely $(OC)_5M{-}{-}CN(CH_2)_nOH$ (M = Cr or W; $n = 2$ or 3) or $(OC)_3Mo(CNCH_2CH_2OH)_3$, are formed exclusively.

However, complexes of type *(A)* with $M = Pd^{II}$ or Pt^{II} are extremely unstable and isomerize immediately to oxazolidin-2-ylidene complexes *(4)* of type *(B)*. Only a yellow coloration of the methylene dichloride phase appearing for a short time during treatment of PdI_2 suspended therein with *(1)* shows



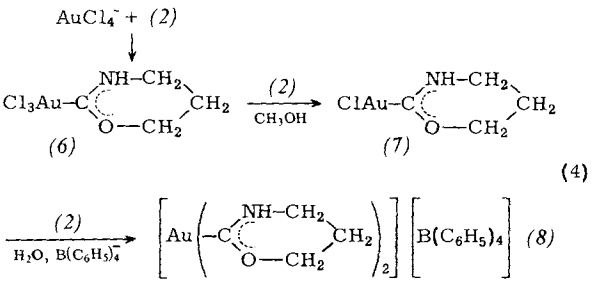
(4) *(5)*

(a): X = Cl; M = Pd, Pt
(b): X = Br, M = Pd
(c): X = I, M = Pd

that *(A)* is involved at all. With the appreciably less reactive *(2)* this intermediate is sufficiently long-lived for its IR spectrum to be recorded: the intense absorption at 2240 cm^{-1} is doubtless that of a complexed isocyanide species $\{Pd^{II}{-}CNCH_2CH_2CH_2OH\}$, which exists together with free *(2)* [ν(NC): 2150 vs, 2167 sh cm^{-1}]. A high Δν(or ν)-value, which can be obtained directly from the spectrum, thus correlates also in this case with a high reactivity of the isocyanide ligand towards nucleophilic reagents[3].

Intermolecular addition of alcohols to coordinated isocyanides seldom succeeds and then only under comparatively energetic reaction conditions[4, 5]. However, the salt-like carbene complexes *(4)* and *(5)* not only form very readily but are also extraordinarily stable and decompose only above 160 °C. Acetone-soluble tetraphenylborates are precipitated from their aqueous solutions on addition of $Na[B(C_6H_5)_4]$. The action of an aqueous-acetone solution of *(4c)* on PdI_2 gives orange-red crystals of $[Pd(oxazolidin\text{-}2\text{-}ylidene)_4][PdI_4]$.

Reaction of $Na[AuCl_4]$ in methanol or water with *(1)* or *(2)* instantaneously yields the sparingly soluble, yellow gold(III)-carbene complexes *(6)*, which are slowly reduced by an excess of isocyanide to the gold(I)-complexes *(7)* and *(8)*.



(4)

Finally, interaction of *(1)* and the stoichiometric amount of $ZnCl_2$, where, as expected, the carbene intermediate *(B)* cannot be stabilized, yields dichlorobis(2-oxazoline)zinc(II) quantitatively, in accord with eq. (3, d).

Tetrakis(oxazolidin-2-ylidene)palladium(II) diiodide (4c):

To a stirred suspension of PdI_2 in a little acetone or methylene dichloride the isocyanide *(1)* is added in the molar ratio 1:4. A yellow solution is formed, from which white, analytically pure *(4c)* is precipitated after a few seconds. The product is washed with acetone and ether and dried in a high vacuum. The yield is almost 100%.

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German version: Angew. Chem. 86, 588 (1974)

[1] *I. Ugi, U. Fetzer, U. Eholzer, H. Knupfer*, and *K. Offermann*, Angew. Chem. 77, 492 (1965); Angew. Chem. internat. Edit. 4, 472 (1965).

[2] Cf.: *U. Schöllkopf* and *R. Jentsch*, Angew. Chem. 85, 355 (1973); Angew. Chem. internat. Edit. 12, 323 (1973).

[3] *J. Chatt, R. L. Richards*, and *G. H. D. Royston*, J. C. S. Dalton *1973*, 1433.

[4] *E. M. Badley, J. Chatt*, and *R. L. Richards*, J. Chem. Soc. *A 1971*, 21; *B. Crociani, T. Boschi*, and *U. Belluco*, Inorg. Chem. 9, 2021 (1970).

[5] *T. Saegusa* and *Y. Ito* in *I. Ugi*: Isonitrile Chemistry. Academic Press, New York 1971, p. 69.

Polynuclear Oxofluoro Anions of Molybdenum(V)[**]

By *Rainer Mattes* and *Gerhard Lux*[*]

$MoOF_5^{2-}$ is the only oxofluoro anion of molybdenum so far recorded in oxidation state +5[1]. By treatment of $MoCl_5$, dissolved in tetrahydrofuran or water-alcohol mixtures, with aqueous solutions of NH_3 and NH_4F (or $N(CH_3)_4F$) we have now obtained the new oxofluoromolybdates(V) $(NH_4)_2MoO_2F_3$ *(1)*, $NH_4MoO_2F_2 \cdot H_2O$ *(2)*, and $N(CH_3)_4MoO_2F_2$ *(3)*. Owing to the possibility of formation of metal-metal bonds these compounds should differ structurally from the corresponding molybdenum(VI) compounds in which only coordination polyhedra (octahedra) linked at corners are found[2, 3]. The large number of strongly electronegative ligands leads one to expect particularly strong metal-metal interaction. Also of interest is the extent to which bonding of the ligands lying opposite to the terminal M—O bonds is weakened by the *trans*-effect[4]—an effect that presumably comes into play in biological redox processes involving Mo^V complexes[5].

The IR and Raman spectra of the anions of the salts *(1)* to *(3)* are largely similar, in spite of the differences in composition. For example, Fig. 1 represents the vibrational spectrum of *(2)*.

The bands at 940—980 cm^{-1} show that only one of the oxygen atoms is bound terminally to the molybdenum atom[1]. The

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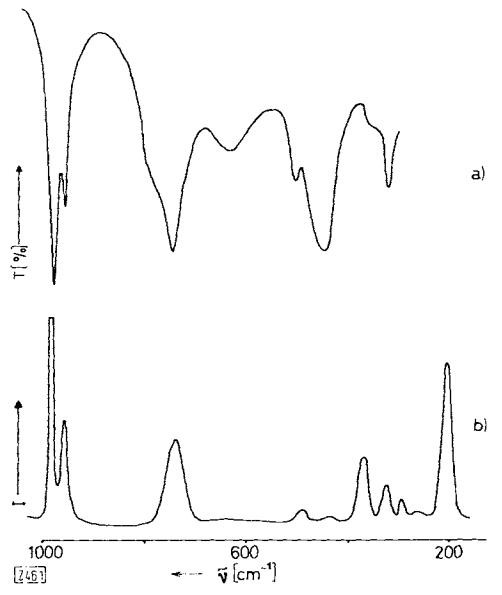
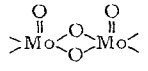


Fig. 1. IR (a) and Raman spectra (b) of $NH_4MoO_2F_2 \cdot H_2O$ (*2*).

broad band at 750cm^{-1} must therefore be due to molybdenum-oxygen bridge bonds[3, 6]. Accordingly all these compounds contain polynuclear complex anions bridged by oxygen atoms. Thus, like $Ba\{[MoO(C_2O_4)H_2O]_2O_2\}$[7], *l*-cysteinato complexes of Mo^{VI}[8] and dilute aqueous Mo^{V} solutions[9], the salts (*1*) to (*3*) very probably contain the binuclear dioxodi-μ-oxodimolybdate(V) groups:



whose residual coordination positions are occupied by F^- and H_2O ligands.

Magnetic investigations gave an effective magnetic moment of 0.58 μ_B for (*1*); (*2*) and (*3*) are diamagnetic. This behavior is explicable by molybdenum-molybdenum interactions where diamagnetism can be achieved by pairing of the two d-electrons with formation of a metal-metal bond[7, 10]. The high intensity band at 200cm^{-1} in the Raman spectrum can be assigned to a metal-metal vibration[11].

Structural investigations are in progress: (*1*) crystallizes orthorhombically with $a=13.60$, $b=7.53$, $c=11.55$ Å, and $Z=8$; (*2*) forms monoclinic crystals with $a=9.33$, $b=13.94$, $c=7.96$ Å, $\beta=113.3°$ and $Z=8$.

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CAS Registry Numbers: (*1*): 52195-83-2 / (*2*): 52195-84-3 / (*3*): 52195-86-5.

[1] *P. C. H. Mitchell*, Quart. Rev. Chem. Soc. *20*, 103 (1966); *D. Grandjean* and *R. Weiss*, Bull. Soc. Chim. Fr. *1967*, 3054.

[2] *R. Mattes*, *G. Müller*, and *H. J. Becher*, Z. Anorg. Allg. Chem. *389*, 177 (1972); *A. Beuter* and *W. Sawodny*, Angew. Chem. *84*, 1099 (1972); Angew. Chem. internat. Edit. *11*, 1020 (1972).

[3] *R. Mattes* and *G. Müller*, Naturwissenschaften *60*, 550 (1973).

[4] *W. R. Scheidt*, Inorg. Chem. *12*, 1758 (1973); *H. Rieskamp* and *R. Mattes*, Z. Anorg. Allg. Chem. *399*, 205 (1973).

[5] Cf.: *A. Kay* and *P. C. H. Mitchell*, J. C. S. Dalton *1973*, 1388; and further references cited therein.

[6] *R. M. Wing* and *K. P. Callahan*, Inorg. Chem. *8*, 971 (1969).

[7] *F. A. Cotton* and *S. M. Morehouse*, Inorg. Chem. *4*, 1377 (1965).

[8] *J. R. Knox* and *C. K. Prout*, Acta Crystallogr. *B25*, 1857 (1969); *M. G. B. Drew* and *A. Kay*, J. Chem. Soc. *A 1971*, 1846.

[9] *M. Ardon* and *P. Pernick*, Inorg. Chem. *12*, 2484 (1973).

[10] *D. H. Brown*, *P. G. Perkins*, and *J. J. Stewart*, J. C. S. Dalton *1972*, 1105.

[11] *J. San Filippo* and *H. J. Sniadoch*, Inorg. Chem. *12*, 2326 (1973).

Synthesis of an all-*cis*-Organocyclotriarsane Derivative[**]

By *Jochen Ellermann* and *Horst Schössner*[*]

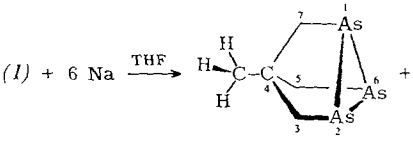
Organo-*cyclohexa*-, *-cyclopenta*- and *-cyclotetra*-arsanes, *e.g.* $(C_6H_5As)_6$[1, 2], $(RAs)_5$ (R = CH_3[2], CF_3[3], C_2H_5, *n*-C_3H_7[2], *n*-C_4H_9, iso-C_4H_9[4]) and $(RAs)_4$ (R = CF_3[3], C_6H_5[5], C_6H_{11}, *sec*-C_4H_9, and *tert*-C_4H_9[4]) have been described previously. The organic substituents of the ring systems are generally in *cis- and trans*-positions[2, 6]. We have now been able to synthesize the first all-*cis*-organo*cyclotri*arsane.

Mass-spectroscopic degradation of tetratertiary organoarsenic compounds leads preferentially to fragment ions containing a cyclotriarsane skeleton[7]. Thus *preparative* production of cyclotriarsane derivatives should be particularly easy starting from the corresponding tritertiary organoarsenic compounds. If (*1*), which can be obtained according to eqs. (1) and (2)[8], is treated with sodium in tetrahydrofuran, then crystalline 4-methyl-1,2,6-triarsatricyclo[2.2.1.0^{2,6}]heptane (*2*) is formed as shown in eq. (3).

$$CH_3C(CH_2Br)_3 + 3\ NaAsR_2 \xrightarrow{\text{liq. } NH_3} CH_3C(CH_2AsR_2)_3 + 3\ NaBr \quad (1)$$

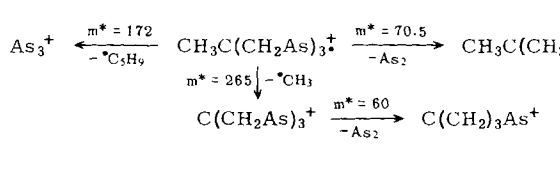
$$CH_3C(CH_2AsR_2)_3 + 6\ HI \xrightarrow{CH_2Cl_2} \underset{(1)}{CH_3C(CH_2AsI_2)_3} + 6\ RH \quad (2)$$

(R = C_6H_5)



(*2*)

The composition and structure of (*2*) are proved by elemental analysis and, especially, by the mass spectrum. The molecular ion M^+ occurs at $m/e=294$ with the relative abundance of 100%; in addition the following fragments are observed: 279 $M-CH_3$ (21%), 239 CH_2As_3 (19%), 225 As_3 (68%), 163 $CHAs_2$ (7%), 150 As_2 (10%), 144 $M-As_2$ (67%), 129 $C(CH_2)_3As$ (38%), 116 C_3H_5As (7%), 101 C_2H_2As (10%), 89 CH_2As (22%), 75 As (6%), 69 $CH_3C(CH_2)_3$ (34%). The most important decomposition steps are shown by the metastable transformations m*:



The cyclotriarsane (*2*) can be sublimed and is readily soluble in THF, diethyl ether, $CHCl_3$, and CH_2Cl_2, moderately soluble in CCl_4, CH_3OH, and light petroleum, but insoluble in benzene. In the ^{1}H-NMR spectrum ($CDCl_3$; TMS internal) two singlets are found, at $\delta=1.38$ (CH_2) and 1.50 ppm (CH_3) in

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[**] Contributions to the Chemistry of Polyfunctional Ligands, Part 29. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. – Part 28: ref. [7].

the intensity ratio 2:1.04. The strongest band in the Raman spectrum, at 300 vs cm^{-1}, is doubtless to be assigned to the (As—As) stretching vibration (A_1) of the three-membered arsenic ring; further, on the assumption of C_{3v} or C_3 molecular symmetry of *(2)*, the resolved medium-strength bands at 252, 246 sh cm^{-1} in the Raman spectrum of solid *(2)* are tentatively assigned to the expected vibration ν(As—As) (E). In the IR spectrum the characteristic ν(As—C)[7-9] (A_1 + E) are observed at 546 and 522 cm^{-1}.

Experimental:

The tris(diiodoarsane) *(1)* (1.11 g, 1.04 mmol) is added portionwise, with stirring, to sodium pellets (0.7 g, 30 mmol) in THF (20 ml). After initial warming, a vigorous reaction sets in; stirring is continued with cooling for 20 min, then the mixture is filtered from undissolved NaI, excess of sodium and decomposition products. The residue is washed three times each with 15 ml of ether, and the solvent is removed from the filtrate at 20 °C in a vacuum. The dried crude product, which still contains NaI, can be purified by sublimation (80—150 °C/0.5 torr): yield 166 mg (54%) of colorless crystals of *(2)*, m.p. 159 °C.

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CAS Registry Numbers: *(1)*: 52196-02-8 / *(2)*: 52196-03-9.

[1] *K. Hedberg, E. W. Hughes*, and *J. Waser*, Acta Crystallogr. *14*, 369 (1961).

[2] *P. S. Elmes, S. Middleton*, and *B. O. West*, Aust. J. Chem. *23*, 1559 (1970); and references cited therein.

[3] *A. H. Cowley, A. B. Burg*, and *W. R. Cullen*, J. Amer. Chem. Soc. *88*, 3178 (1966); *R. C. Dobbie* and *R. G. Carell*, Inorg. Chem. *6*, 1450 (1967).

[4] *A. Tzschach* and *V. Kiesel*, J. Prakt. Chem. *313*, 259 (1971).

[5] *M. Green* and *D. Kirkpatrick*, J. Chem. Soc. *A 1968*, 483.

[6] *J. H. Burns* and *J. Waser*, J. Amer. Chem. Soc. *79*, 859 (1957); *E. Wells, R. C. Fergusson, J. C. Hallett*, and *L. K. Peterson*, Can. J. Chem. *46*, 2733 (1968).

[7] *J. Ellermann, H. Schössner, A. Haag*, and *H. Schödel*, J. Organometal. Chem. *65*, 33 (1974).

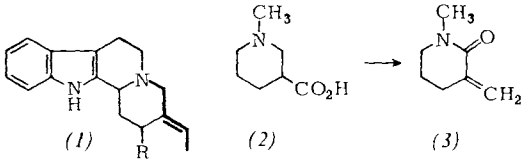
[8] *J. Ellermann* and *H. Schössner*, unpublished work.

[9] *D. M. Revitt* and *D. B. Sowerby*, Spectrochim. Acta *26 A*, 1581 (1970); J. Chem. Soc. *A 1970*, 1218.

Stereoselective Synthesis of Exocyclic Trisubstituted Double Bonds[1][**]

By *Dietrich Thielke, Joachim Wegener*, and *Ekkehard Winterfeldt*[*]

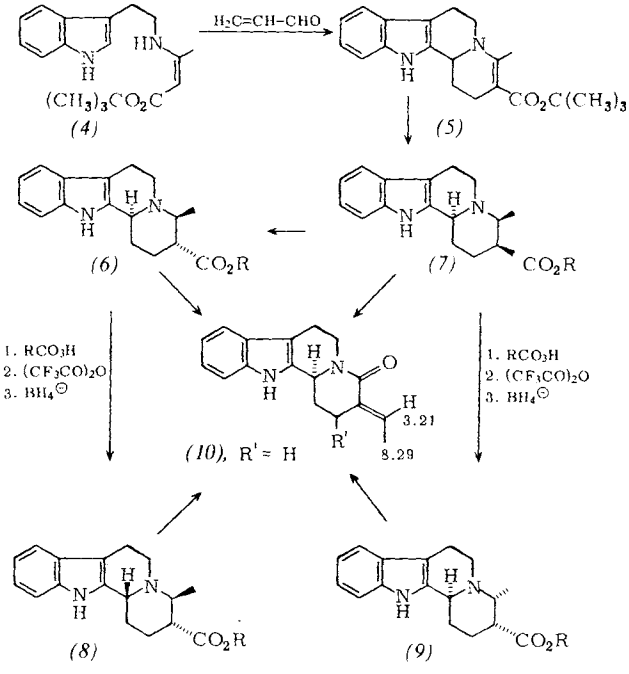
Exocyclic trisubstituted double bonds as shown in *(1)* occur in many indole alkaloids[2] as a characteristic structural unit.



(1) *(2)* *(3)*

We have attempted to exploit the rearrangement of piperidinecarboxylic acids *(2)* to unsaturated lactams *(3)*[3,4] in the case of substituted indoloquinolizidines as a means of synthesizing compounds of type *(1)*. Publication of the mechanism of the reaction *(2)*→*(3)*, and of successful attempts to rearrange also substituted piperidines of similar kind (which, however, gave both the stereoisomeric olefins), by *Rapoport et al.*[5] has induced us now to release our results, which reveal the high stereoselectivity of the reaction in polycyclic systems.

When the enamine from tryptamine and *tert*-butyl acetoacetate *(4)* is warmed with acrolein and then set aside in glacial acetic acid it affords the vinylogous urethan *(5)*[7]. On reduction thereof with $NaBH_4$ in glacial acetic acid[6], *(7a)* is obtained smoothly and with high stereoselectivity. The configuration follows from spectral data and from the convertibility into *(6a)* on treatment with potassium *tert*-butoxide. *(6a)* and *(7a)* afford the epimers *(8a)* and *(9a)*, respectively, by way of the *N*-oxide, a Polonovski reaction to give the tetrasubstituted immonium salt, and subsequent reduction by $NaBH_4$. All four compounds can be cleaved by trifluoroacetic acid at room temperature to the acids *(6b)* to *(9b)* with retention of configuration (re-esterification regenerates the starting ester of unchanged configuration).



(a), R = $C(CH_3)_3$; *(b)*, R = H

When warmed in acetic anhydride all four acids yield exclusively the same unsaturated lactam *(10)*, R′ = H, in good yield. The configuration at the double bond follows from the NMR data (for τ values see the formula), which are particularly convincing when compared with the values for the isomeric lactam obtained in minute amounts from the mother liquor (vinyl-H: τ = 4.14; methyl-H: τ = 7.96).

Reducing the unsaturated lactam with diisobutylaluminum hydride in monoglyme affords the base *(1)*, R = H. Applicability also to trisubstituted compounds follows from conversion of the enamine of type *(5)* (obtainable from crotonaldehyde) into the unsaturated lactam *(10)*, R′ = CH_3.

It thus appears that during these rearrangements each of the intermediates isomerizes to the thermodynamically stable *trans*-configuration. The unsaturated lactams *(10)*, R′ = H, and *(10)*, R′ = CH_3, are constitutionally and configurationally stable under the conditions of the reaction.

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CAS Registry Numbers:
(4): 52225-68-0 / *(5)*: 52225-69-1 / *(6a)*: 52225-45-3 / *(6b)*: 52225-46-4 / *(7a)*: 52248-68-7 / *(7b)*: 52248-69-8 / *(8a)*: 52248-70-1 / *(8b)*: 52248-71-2 / *(9a)*: 52248-72-3 / *(9b)*: 52248-73-4 / *(10)* (R' = H): 52225-47-5 / *(10)* (R' = Me): 52225-70-4.

[1] Reactions of Indole Derivatives, Part 23.—Part 22: *J. D. Wilcock* and *E. Winterfeldt*, Chem. Ber. *107*, 975 (1974).

[2] *M. Hesse*: Indolalkaloide in Tabellen. Springer Verlag, Berlin 1964.

[3] *M. Ferles*, Collect. Czech. Chem. Commun. *29*, 2323 (1964).

[4] *C. Tang* and *H. Rapoport*, J. Amer. Chem. Soc. *94*, 8615 (1972).

[5] *D. L. Lee, C. J. Morrow*, and *H. Rapoport*, J. Org. Chem. *39*, 893 (1974).

[6] *C. Djerassi, H. J. Monteiro, A. Walser*, and *L. J. Durham*, J. Amer. Chem. Soc. *88*, 1792 (1966).

[7] All the substances were characterized by IR, NMR, and mass spectra and correct elemental analyses.

Hexamanganato(VII)manganic(IV) Acid: A "Pseudopermanganic Acid"[**]

By *Bernt Krebs* and *Klaus-Dieter Hasse*[*]

If an aqueous solution of permanganic acid (prepared by reaction of stoichiometric amounts of $Ba(MnO_4)_2$ with H_2SO_4) is concentrated under reduced pressure, one obtains different products, depending upon the experimental conditions: dimanganese heptoxide, water, manganese dioxide phases (with liberation of oxygen), and a new crystalline compound which has not yet been exactly identified[1]. On the basis of chemical analysis and its redox equivalent, the substance was assumed to be a "solid permanganic acid" having the composition $Mn_2O_7 \cdot 2H_2O$[1]. This violet compound is thermally very sensitive and decomposes mainly to Mn_2O_7, oxygen, manganese dioxides, and water above $-4\,^{\circ}C$, reacts vigorously with oxidizable substances, but can be obtained pure as large bipyramidal crystals under optimal reaction conditions (distillation at $-40\,^{\circ}C/10^{-3}$ torr, cf. ref. [1]).

X-Ray structure analysis at $-120\,^{\circ}C$ has now shown that the compound concerned is a complex hexamanganato(VII)-manganic(IV) acid; the redox equivalent per Mn (6.57) corresponding to the exact formula $(H_3O)_2[Mn(MnO_4)_6] \cdot 11H_2O$ *(1)* approaches that of a "true" permanganic acid.

In the $[Mn(MnO_4)_6]^{2-}$ anion, a central Mn^{IV} atom, which is surrounded octahedrally by bridging O atoms, is coordinated with six $Mn^{VII}O_4$ tetrahedra with a trigonal prismatic arrangement of the Mn^{VII} relative to the central Mn^{IV}; the complete anion approximates well to C_2 symmetry. The mean bond lengths amount to Mn^{IV}—O(bridge) 1.90 (individual values between 1.85 and 1.94), Mn^{VII}—O(bridge) 1.74 (1.69 to 1.75), Mn^{VII}—O(terminal) 1.60 Å (1.55 to 1.66 Å).

The hexamanganato(VII)manganate(IV) ion (Fig. 1) represents a new type of a "heteropolyanion" in which both components arise from the same element in different oxidation states. The chemical properties are largely determined by the Mn^{VII} centers present in excess.

The excess protons are clearly present as H_3O^+ ions, which are linked to the other H_2O molecules of the lattice by a hydrogen bond system (O(H)···O distances in the bridges originating from the H_3O^+ groups between 2.48 and 2.60 Å). Crystal data of compound *(1)* (cf. ref. [1]): orthorhombic, C_{2v}^{19}-Fdd2; $a = 17.77(2)$, $b = 63.97(8)$, $c = 10.48(2)$ Å (at $-120\,^{\circ}C$); $Z = 16$; $d_{calc.} = 2.24\,g\,cm^{-3}$. The structure was determined from 1457 film data and refined to $R = 0.092$.

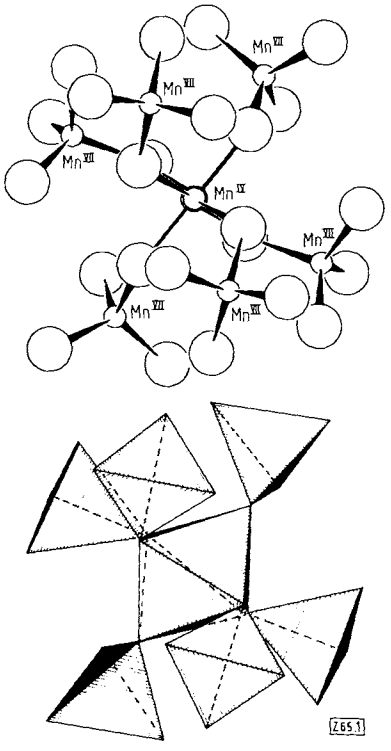


Fig. 1. Structure of the $[Mn(MnO_4)_6]^{2-}$ anion in solid hexamanganato(VII)-manganic(IV) acid $(H_3O)_2[Mn(MnO_4)_6] \cdot 11H_2O$ *(1)*.

The behavior of aqueous permanganic acid solutions on concentration under various conditions will be reported at a later date. The question of the existence of a pure "solid permanganic acid" still remains open. However, results obtained so far, the behavior of Mn_2O_7[2] towards water, and crystallochemical considerations cast doubt upon the stability of a solid phase in the Mn_2O_7—H_2O system (as hydrate $Mn_2O_7 \cdot xH_2O$ or, as formerly postulated, as $HMnO_4$ or as $H_3O^+MnO_4^-$[3]).

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German version: Angew. Chem. *86*, 647 (1974)

[1] *B. Krebs* and *K.-D. Hasse*, Z. Naturforsch. *28b*, 218 (1972), in which publication 0.5 mM should read 0.5 M (beginning of third paragraph), and −18 C should read −180 C (end of third paragraph).

[2] *O. Glemser* and *H. Schröder*, Z. Anorg. Allg. Chem. *271*, 293 (1953).

[3] *N. A. Frigerio*, J. Amer. Chem. Soc. *91*, 6200 (1969).

Cyclooctasulfur Monoxide from Cyclooctasulfur[1]

By *Ralf Steudel* and *Jörg Latte*[*]

Cyclooctasulfur monoxide was first obtained as a product of the reaction of thionyl chloride with "crude sulfane" H_2S_n[2]. We have now found that cyclooctasulfur can be oxidized directly with trifluoroperacetic acid (molar ratio 1:1) in a simple manner:

$$S_8 + CF_3CO_3H \rightarrow S_8O + CF_3SO_2H$$

The S_8O obtained in *ca.* 45% yield by this method is identical in color, crystal form, decomposition temperature, solubility,

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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

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composition, and IR spectrum[3] with the product prepared from $SOCl_2$ and H_2S_n. This new, more productive synthetic route requires much less time and experimental effort than the former preparation.

Procedure:

S_8 (3.76 g, 14.7 mmol) is dissolved in CH_2Cl_2 (800 ml) by refluxing. The homogeneous solution is slowly cooled to 0 °C and protected from light by a black cloth. A freshly prepared solution of trifluoroperacetic acid [obtained by suspension of 50% H_2O_2 (1 g, 14.7 mmol) in CH_2Cl_2 (50 ml) at 0 °C and rapid addition of trifluoroacetic anhydride (5 ml, 36 mmol)] is added dropwise over 1 h to the stirred reaction mixture, which assumes an intense yellow hue. Concentration in a vacuum at 20 °C bath temperature to 1/3 of the original volume leads to precipitation. Further crystallization is induced by cooling to −20 °C. The precipitate is collected on a glass frit, washed with CH_2Cl_2, and dried in a vacuum. The procedure yields 1.8 g of almost pure S_8O which can be isolated analytically pure by recrystallization from CS_2.

Received: May 3, 1974 [Z 67 IE]
German version: Angew. Chem. 86, 648 (1974)

[1] Sulfur-Oxygen Compounds, Part 23.—Part 22 is considered to be: *H. Bock, B. Solouki, P. Rosmus,* and *R. Steudel*, Angew. Chem. *85*, 987 (1973); Angew. Chem. internat. Edit. *12*, 933 (1973).—Part 21: [3].

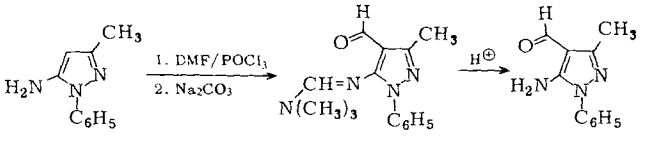
[2] *R. Steudel* and *M. Rebsch*, Angew. Chem. *84*, 344 (1972); Angew. Chem. internat. Edit. *11*, 302 (1972); *R. Steudel, P. Luger, H. Bradaczek*, and *M. Rebsch, ibid. 85*, 452 (1973) and *12*, 423 (1973), resp.

[3] *R. Steudel* and *M. Rebsch*, J. Mol. Spectrosc. *51*, 334 (1974).

Synthesis of Pyrazolo Heteroaromatic Compounds by Means of 5-Amino-3-methyl-1-phenylpyrazole-4-carbaldehyde

By *Jochen Häufel* and *Eberhard Breitmaier*[*]

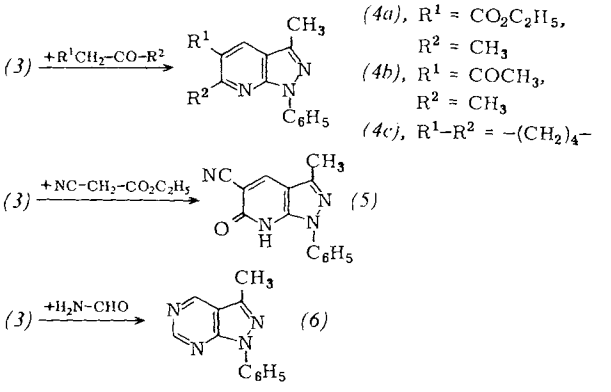
5-Amino-3-methyl-1-phenylpyrazole-4-carbaldehyde *(3)* is formed in a modified Vilsmeyer synthesis[1,2]: reaction of 5-amino-3-methyl-1-phenylpyrazole *(1)*[3] with an excess of *N,N*-dimethylformamide (DMF) and phosphorus oxide chloride affords crystalline 5-[(*N,N*-dimethylamino)methyleneamino]-3-methyl-1-phenylpyrazole-4-carbaldehyde *(2)*, which is converted in good yield into *(3)* by acid hydrolysis.



(1) *(2)* *(3)*

This new aldehyde opens a direct route for preparation of condensed heterocycles of the pyrazole series. Thus cyclocondensation of *(3)* with 1,3-dicarbonyl compounds affords the pyrazolo[3,4-*b*]pyridines *(4a)—(4c)*, with ethyl cyanoacetate affords the derivative *(5)* and with formamide the pyrazolo[3,4-*d*]pyrimidine *(6)*. The condensation product of *(3)* with cyclohexanone is identical with 5,6,7,8-tetrahydropyrazolo[3,4-*b*]quinoline *(4c)* prepared from 2-hydroxymethylenecyclohexanone and *(1)*[4]. The compounds prepared were identified by means of spectroscopic data (IR, UV, MS, and ^{1}H- and ^{13}C-NMR).

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5-Amino-3-methyl-1-phenylpyrazole-4-carbaldehyde (3):

$POCl_3$ (1.5 mol) is added dropwise with cooling to DMF (3.5 mol). Then *(1)* (0.5 mol) is added portionwise, the reaction mixture is stirred for 17 h at 70 °C (oil-bath temperature) and subsequently poured cautiously into an excess of Na_2CO_3 solution (cooling). The crystals that separate after some time [*(2)*] are hydrolyzed by HCl (*ca.* 20 wt.-%). After 50 hours' stirring at 40 °C (oil-bath temperature), neutralization with Na_2CO_3 solution, extraction with ether and removal of the solvent, *(3)* is obtained as a viscous oil. Recrystallization from 2-propanol affords a finely crystalline, pale yellow product: yield 64%, m.p. 97.5 °C.

Pyrazolo[3,4-b]pyridine (4) and 6,7-dihydro-3-methyl-6-oxo-1-phenylpyrazolo[3,4-b]pyridine-5-carbonitrile (5):

The CH-acidic carbonyl compound (0.02 mol) is refluxed with 0.02 mol of *(3)* in glacial acetic acid (30 ml) for *ca.* 30 h. For working-up, the mixture is poured into an excess of Na_2CO_3 solution and extracted with ether. The crude products are recrystallized from ethanol or ethanol/water [*(4a)*, yield 68%, m.p. 79.5 °C; *(4b)*, yield 79%, m.p. 96 °C; *(4c)*[4], yield 46%, m.p. 86 °C; *(5)*, yield 81%, m.p. 316 °C].

3-Methyl-1-phenylpyrazolo[3,4-d]pyrimidine (6):

0.025 mol of *(3)* is heated with 0.1 mol of formamide for 20 h at 140 °C. The cooled reaction mixture is treated with water (10 ml) and extracted with chloroform. The oil remaining on removal of the solvent is crystallized from 2-propanol; yield 60%, m.p. 84 °C.

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CAS Registry Numbers:
(1): 1131-18-6 / *(3)*: 52217-35-3 / *(4a)*: 52217-36-4 / *(4b)*: 52217-37-5 / *(4c)*: 51431-29-9 / *(5)*: 52217-38-6 / *(6)*: 52217-39-7 / ethyl 3-oxobutanoate: 141-97-9 / 2,4-pentanedione: 123-54-6 / cyclohexanone: 108-94-1 / ethyl cyanoacetate: 105-56-6 / formamide: 75-12-7.

[1] Organikum. VEB Deutscher Verlag der Wissenschaften, Berlin 1970, pp. 358 ff.

[2] *A. Vilsmeyer*, Chem.-Ztg. *75*, 133 (1951).

[3] *E. Mohr*, J. Prakt. Chem. *79*, 14 (1909).

[4] *J. Häufel* and *E. Breitmaier*, Angew. Chem. *85*, 959 (1973); Angew. Chem. internat. Edit. *12*, 922 (1973).

Conformation of *trans*-Cyclooctene

By *Otto Ermer*[*]

Previous X-ray structural studies have not hitherto given exact structural parameters for *trans*-cyclooctene derivatives[1]

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because of unfavorable experimental conditions. In addition, in two of the compounds studied the *trans*-cyclooctene double bond, which is highly non-planar, is coordinated to heavy metal atoms[1], and this complicates conclusions about the structure of *trans*-cyclooctene itself. The X-ray structure analysis of *trans*-2-cyclooctenyl 3',5'-dinitrobenzoate *(1)* (Fig. 1d) described below is free from these disadvantages.

We undertook the X-ray crystal structure investigation in order to test our force-field calculations[2] experimentally, which in the case of *trans*-cyclooctene contradicted the results of a

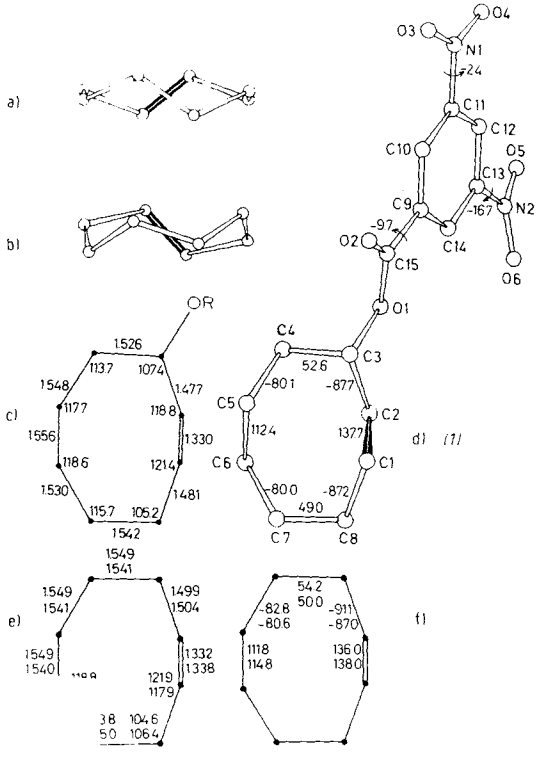


Fig. 1. a) Crown conformation and b) distorted chair conformation of *trans*-cyclooctene (symmetry C_2 in both cases). c) Observed bond lengths [Å] and angles [°] and d) torsion angles [°] (view perpendicular to the best plane through the eight-membered ring of C atoms) of the eight-membered ring in *(1)* (estimated average standard deviations: 0.004 Å, 0.3° and 0.3°, respectively: R = 3,5-dinitrobenzoyl); e) and f) comparison with gas electron diffraction results [4] (upper values) and results of our force field calculations (lower values): ring symmetry C_2.

gas electron diffraction analysis by *Gavin* and *Wang*[3]. From their results these authors deduced a distorted chair conformation (symmetry C_2, Fig. 1b), whereas according to our calculations the crown conformation (symmetry C_2, Fig. 1a) is the more stable by 3.1 kcal mol^{-1}. The data of a gas electron diffraction analysis by *Traetteberg*[4] have been interpreted in favor of the crown conformation (Fig. 1a).

Crystal data of *(1)*[**]: $a = 10.963(2)$, $b = 5.656(1)$, $c = 14.873(2)$ Å; $\alpha = 104.91(1)$, $\beta = 122.75(1)$, $\gamma = 76.18(1)°$; space group $P\bar{1}$; $Z = 2$. The intensities of 2774 reflections were measured (four-circle diffractometer, $\sin\theta/\lambda \leq 0.639$ Å^{-1}, $Mo_{K\alpha}$ radiation, $\lambda = 0.71069$ Å). The structure was solved by inspection of a sharpened Patterson function of the crystal. Figures 1 and 2 show the results obtained for the eight-membered ring after refinement [1623 reflections with $F_0 \geq 3\sigma(F_0)$; full matrix; C, N, O anisotropic; H isotropic (one common temperature factor, fixed parameters of the heavier atoms, exclusion of reflections with $\sin\theta/\lambda \geq 0.45$ Å^{-1}); $R = 0.052$].

[**] We thank Dr. *G. H. Whitham*, Oxford, for a sample.

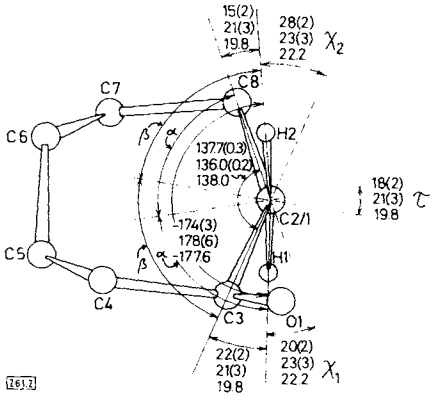


Fig. 2. Torsion and out-of-plane bending angles [°] at the double bond (projection along $C^2{=}C^1$; τ and χ are explained in the text: α and β are auxiliary angles for explanation of the Figure). Upper values: X-ray analysis of *(1)* (estimated standard deviations in parentheses); middle values: gas electron diffraction [4]: lower values: calculated [2].

The carbon skeleton of *trans*-cyclooctene in the crystals of *(1)* possesses the crown conformation with closely approximated C_2 symmetry (Figs. 1c and 1d). Bond lengths, bond angles, and torsion angles agree satisfactorily with *Traetteberg*'s results[4] and our calculations[2] (Figs. 1e and 1f). This holds also for the results of three previous studies[1] insofar as the experimental uncertainties allow comparisons. In particular, and remarkably, the C—C=C—C torsion angle [137(0.3)°; Figs. 1d and 2] and the corresponding angles in the Cu and Pt complexes (134 and 137°, respectively) are very similar. The C—C=C—C torsion angle determined from *Gavin* and *Wang*'s data[3] for the distorted chair conformation amounts to 157°, whereas our calculated value for this conformation is 137.9°; this large discrepancy does not support the view[3] that these older gas electron diffraction data were obtained from a sample of *trans*-cyclooctene possessing the distorted chair conformation, which according to our calculations is less stable, although the energy barrier between the two forms is perhaps large enough to prevent their equilibration[***].

The length of the double bond in the eight-membered ring, being 1.330 Å, is normal in spite of the marked deviation from planarity. Three independent geometric parameters are necessary to describe non-planar distortions of double bonds[2]. We choose the angle of pure twisting τ, which amounts to 18(2)°, and the two out-of-plane bending angles χ_1 and χ_2 [20(2)° at C^1 and 28(2)° at C^2: Fig. 2]. τ is defined as the arithmetical mean of the two H—C=C—C torsion angles, and χ as the supplementary angle of the dihedral angle between the planes of the H—C=C and the C—C=C angles at the same double-bond C atom. The deviation of the C—C=C—C torsion angle from 180° [42.3(0.3)°] is thus composed of 18(2)° pure twisting and of 24(2)° out-of-plane bending (Fig. 2). Obviously the double bond parameters involving H atoms cannot be determined accurately from X-ray data. However, the bending deformations of the double-bond H atoms towards the inner part of the ring are highly significant. All the geometrical details observed for the double bond agree well with the more recent gas electron diffraction results[4] and with our force field calculations (Fig. 2). The essentially harmonic potentials for twisting and out-of-plane

[***] *Note added in proof* (August 19, 1974): We have recently calculated an energy profile for the crown-distorted chair interconversion which does not show an energy barrier large enough to prevent equilibration at room temperature.

bending of a double bond[2] in our olefin force field thus appear to be useful for deformations up to at least 20°.

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German version: Angew. Chem. 86, 672 (1974)

CAS Registry Numbers:
(1): 42848-27-1 / *trans*-cyclooctene: 931-89-5.

[1] Complex with CuCl: *P. Ganis, U. Lepore*, and *E. Martuscelli*, J. Phys. Chem. *74*, 2439 (1970); complex with $PtCl_2$ and α-methylbenzylamine: *P. C. Manor, D. P. Shoemaker*, and *A. S. Parkes*, J. Amer. Chem. Soc. *92*, 5260 (1970); 3-iodo-5-nitrobenzoate of *trans*-2-cyclooctenol: *G. Ferguson* and *D. Hawley*, personal communication.

[2] *O. Ermer* and *S. Lifson*, J. Amer. Chem. Soc. 95, 4121 (1973).

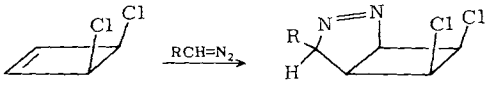
[3] *R. M. Gavin* and *Z. F. Wang*, J. Amer. Chem. Soc. *95*, 1425 (1973).

[4] *M. Traetteberg*, Fifth Austin Symposium on Gas Phase Molecular Structure, Austin, Texas, March, 1974; *M. Traetteberg*, personal communication.

Stereospecific *endo-anti*-Cycloaddition of Diazoalkanes to 7-Substituted Norbornadiene: A π→σ* Effect?

By *Michel Franck-Neumann* and *Madjid Sedrati*[*]

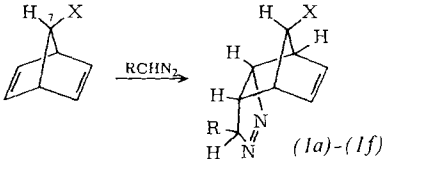
Reaction of diazomethane or diazoethane with *cis*-3,4-dichlorocyclobutene gives *syn*-pyrazolines quantitatively[1] This



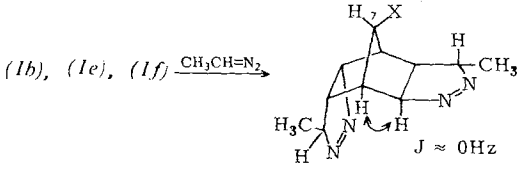
R = H, CH_3

astonishing stereospecific cycloaddition induced us to carry out similar investigations with the norbornadiene system.

With diazoalkanes *cis-endo-* and *trans*-dichloronorbornene[2] give only *exo*-adducts[3], as is shown by the very small coupling constants of the bridgehead and pyrazoline protons[4]. The



(1a)-(1f)



(2b), (2e), (2f)

Table 1. Cycloadducts of types *(1)* and *(2)* prepared.

Cpd.	R	X	*(1)* M.p. [°]	*(1)* Yield [%]	*(2)* Decomp. [°C]
(a)	H	Cl	64	35	
(b)	CH_3	Cl	71	80	110
(c)	CH_3	Br	86	80	
(d)	CH_3	I	53	75	
(e)	CH_3	OAc	90 (dec.)	[a]	140
(f)	CH_3	OH		[a]	150

[a] See text.

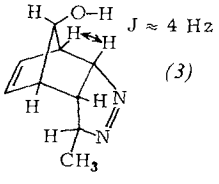
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upfield shift for the C^7 proton in *syn*-position to the azo group is large, being 0.8—1.0 ppm.

The reaction of 7-chloronorbornadiene[5] with diazomethane or diazoethane proceeds differently: the 1-pyrazolines *(1a)* and *(1b)*, respectively [ν(N=N)≈1550 cm^{-1}] which are the sole products (NMR) have *endo*-stereochemistry, as follows from the coupling constants of the bridgehead and pyrazoline protons (≈4.5 Hz)[4]. In the presence of a large excess of diazoethane, *(1b)* then undergoes a further cycloaddition which leads to the *endo-exo*-bispyrazoline *(2b)* [isolated 24%; 75% calculated on the amount of *(1b)* reacting]. Since this barely alters the chemical shift of the C^7 proton [*(1b)*: δ = 3.87 ppm; *(2b)*: 3.78 ppm], it must be assumed that the *exo*-group is *anti* to this proton and consequently that the preceding *endo*-cycloaddition at the double bond occurs *anti* to the 7-chloro substituent (Table 1).

With diazoethane, 7-bromo-[6] and 7-iodo-norbornadiene[7] undergo the same stereospecific *endo-anti*-cycloadditions, affording *(1c)* and *(1d)*, respectively. In the case of norbornadienyl acetate[8] the second cycloaddition occurs approximately as fast as the first, so that a 1:1 mixture of *(1e)* and *(2e)* is formed (56%).

Norbornadien-7-ol[5a] gives, alongside the *endo-anti*-adduct *(1f)*, the bisadduct *(2f)* and the *endo-syn*-pyrazoline *(3)* (m. p. 87 °C; proportions 1.3:1:1; total yield 50%). 7-*tert*-Butoxynorbornadiene[9] and diazoethane, however, afford only an *exo*-adduct—probably the *syn*-isomer.



(3)

These "contrathermodynamic"[10] *endo-anti*-cycloadditions can no longer be explained as being due to an attractive interaction in the transition state between the nitrogens of the diazoalkanes and the chlorine atom[11] or, generally, the C^7-substituent. Now, however, a direct interaction is conceivable between the highest occupied, relatively high-lying π-orbital of the norbornadiene and the low-lying antibonding σ*-orbital of the C—X bond (X electronegative), whereby the *anti*-double bond becomes electron-poor, thus influencing the orientation of the reaction (Fig. 1).

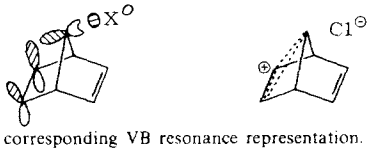


Fig. 1. π→σ* Interaction and corresponding VB resonance representation.

The *endo-syn*-cycloaddition to norbornadien-7-ol can in its turn be explained as involving an intramolecular hydrogen bond[5a, 8], the *syn*-double bond acting in a dative capacity.

Ab initio calculations show that the highest occupied MO of 7-chloronorbornadiene is localized mainly on the chlorine side, but without participation of an antibonding σ*-C—Cl orbital[11]. Since in the frontier orbital model the reactivity in the 1,3-dipolar cycloadditions with diazoalkanes is determined mainly by the HOMO-dipole-LUMO-dipolarophile interaction[12], we consider that a further interaction in this orientation complex with the σ*-orbital provides a better explanation of this *endo-anti*-addition. A formal similarity with anionic hyperconjugation[13] or the anomer effect[14]

can be recognized if one writes a transition state with localized partial charges (Fig. 2).

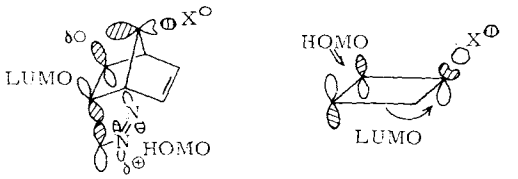


Fig. 2. p→σ* Interactions.

These considerations also apply to additions of diazoalkanes[11] and to the stereospecific Diels-Alder additions to *cis*-3,4-dichlorocyclobutene[15] (Fig. 2). Other stereospecific reactions—mostly cycloadditions—can probably also be explained by interactions with low-lying antibonding orbitals.

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CAS Registry Numbers:
(1a): 52217-24-0 / *(1b)*: 52217-25-1 / *(1c)*: 52217-26-2 / *(1d)*: 52217-27-3 / *(1e)*: 52217-28-4 / *(1f)*: 52217-29-5 / *(2b)*: 52217-30-8 / *(2e)*: 52217-31-9 / *(2f)*: 52217-32-0 / *(3)*: 52248-52-9 / diazomethane: 334-88-3 / diazoethane: 1117-96-0 7-chloronorbornadiene: 1609-39-8 / 7-bromonorbornadiene: 52217-33-1 / 7-iodonorbornadiene: 52217-34-2 / 7-norbornadienyl acetate: 13426-49-8 / 7-norbornadienol: 822-80-0.

[1] *M. Franck-Neumann*, Angew. Chem. *81*, 189 (1969); Angew. Chem. internat. Edit. *8*, 210 (1969).

[2] *K. Alder* and *H. F. Rickert*, Liebigs Ann. Chem. *543*, 1 (1940); *P. D. Bartlett, R. Helgesson*, and *O. A. Wersel*, Pure Appl. Chem. *16*, 187 (1968).

[3] *M. Sedrati*, Dissertation, Strasbourg 1974; *M. Franck-Neumann* and *M. Sedrati*, Org. Magn. Resonance *5*, 217 (1973).

[4] *P. Lazlo* and *P. von R. Schleyer*, J. Amer. Chem. Soc. *86*, 1171 (1964).

[5] a) *S. Winstein* and *C. Ordronneau*, J. Amer. Chem. Soc. *82*, 2084 (1960); b) *P. R. Story* and *M. Saunders*, *ibid. 84*, 4876 (1962).

[6] 7-Bromonorbornadiene is obtained in 26% yield from norbornadien-7-ol and dibromotriphenylphosphorane [3].

[7] 7-Iodonorbornadiene is obtained in 46% yield from 7-chloronorbornadiene and sodium iodide [3].

[8] *P. R. Story*, J. Org. Chem. *26*, 287 (1961).

[9] *P. R. Story* and *S. R. Fahrenholtz*, Org. Synth. *44*, 12 (1964); cf. addition of phenyl azide: *G. W. Klumpp, A. H. Veefkind, W. L. de Graaf*, and *F. Bickelhaupt*, Liebigs Ann. Chem. *706*, 47 (1967).

[10] *R. Huisgen, R. Grashey*, and *J. Sauer* in *S. Patai*: The Chemistry of Alkenes. Interscience, New York 1964, p. 739; *P. von R. Schleyer*, J. Amer. Chem. Soc. *89*, 701 (1967).

[11] *G. Wipff*, Strasbourg, unpublished work.

[12] *R. Sustmann*, Tetrahedron Lett. *1971*, 2717.

[13] *R. Hoffmann, L. Radom, J. A. Pople, P. von R. Schleyer, W. J. Hehre*, and *L. Salem*, J. Amer. Chem. Soc. *94*, 6221 (1972).

[14] *C. Romers, C. Altona, H. R. Buys*, and *E. Havinga*, Top. Stereochem. *4*, 73 (1969).

[15] *M. Avram, I. G. Dinulescu, G. M. D. Mateescu*, and *C. D. Nenitzescu*, Rev. Roumaine Chim. *13*, 505 (1968).

1,3,2,4-Diazadistannetidines, the First Four-Membered Cyclostannazanes

By *Dieter Hänssgen* and *Inge Pohl*[*]

The unusual properties of compounds containing the *tert*-butyltin group attached to an inorganic element[1, 2] are shown by, *inter alia*, the action of di-*tert*-butylstannylbis(dimethylamine) *(1)* on an excess of methyl- or benzyl-amine. Unlike other diorganostannylbis(dialkylamines), which react to form cyclotristannazanes[3], *(1)* affords the stannylamine *(2)* which condenses at 100 to 130 °C with loss of alkylamine to yield

$$(t\text{-}C_4H_9)_2Sn[N(CH_3)_2]_2 + 2\ RNH_2 \longrightarrow (t\text{-}C_4H_9)_2Sn(NHR)_2 + 2\ (CH_3)_2NH$$
(1) *(2)*

$$2\ (2) \longrightarrow (t\text{-}C_4H_9)_2Sn\langle N(R)\rangle Sn(t\text{-}C_4H_9)_2 + 2\ R\text{-}NH_2$$
(3)

(a), R = CH_3; *(b)*, R = $C_6H_5CH_2$

the novel 1,3,2,4-diazadistannetidines *(3a)* and *(3b)*, respectively. *(3a)* and *(3b)* form colorless crystals that are sensitive to hydrolysis and dissolve readily in aromatic and aliphatic hydrocarbons.

Whereas the eight-membered heterocycle *(4)* (m.p. 220 °C) is formed from *(3a)* and, *e.g.*, benzonitrile by 1,2-dipolar addition and ring expansion, reaction with sulfur-containing heterocumulenes such as carbon disulfide and phenyl isothiocyanate affords the dithiadistannane *(5)* and isothiocyanate or carbodiimide, respectively.

$$(3a) + 2\ C_6H_5CN \longrightarrow (t\text{-}C_4H_9)_2Sn\langle N(C_6H_5)\text{-}C(=N\text{-}CH_3)\rangle Sn(t\text{-}C_4H_9)_2$$
(4)

$$(3a) + 2\ R'\text{=}C\text{=}S \longrightarrow (t\text{-}C_4H_9)_2Sn\langle S\rangle Sn(t\text{-}C_4H_9)_2 + 2\ R'\text{=}C\text{=}N\text{-}CH_3$$
(5) R' = S or C_6H_5N

The composition and structure of *(3a)*, *(3b)*, and *(4)* were proved by elemental analysis, molecular weight determination (cryoscopic in benzene) and IR, ^{1}H-NMR, and mass spectra. ^{1}H-NMR spectra (measured at 37 °C in C_6D_6, TMS intern., δ values); *(3a)*: *t*-C_4H_9 = −1.07 ($J_{^1H\text{-}C\text{-}^{117,119}Sn}$ = 74/76 Hz); H_3CN = −2.95 ($J_{^1H\text{-}C\text{-}N\text{-}^{117,119}Sn}$ = 49/51 Hz). *(3b)*: *t*-C_4H_9 = −1.22 ($J_{^1H\text{-}C\text{-}^{117,119}Sn}$ = 73.5/77 Hz); H_2C = −4.44 ($J_{^1H\text{-}C\text{-}N\text{-}^{117,119}Sn}$ = 45/47 Hz); C_6H_5 = −7.42 to −7.12 (m). Mass spectra (selection) (*m/e*): *(3a)*: 526 (molecular ion); 469, 412, 355, 298 (rel. int. 100%), corresponding to M − 1, 2, 3, and 4 *t*-C_4H_9, respectively; 269 Sn—$N(CH_3)$—Sn. *(3b)*: 678 (molecular ion); 621, 564 (rel. int. 100%), 507, 450, corresponding to M − 1, 2, 3, and 4 *t*-C_4H_9, respectively; 345 Sn—$N(CH_2C_6H_5)$—Sn. The fragments are given only for ^{120}Sn.

(5) was identified by comparison with a sample prepared in a different way[4].

1,3-Disubstituted 2,4-di-tert-butyl-1,3,2,4-diazadistannetidines (3)

A primary amine (20 mmol) is dropped into *(1)* (3.21 g, 10 mmol) at 0 °C, and the whole is then warmed slowly to 120 °C (3 h). Sublimation of the crude product at 120 °C/0.2 torr affords 2.35 g (94%) of *(3a)* as colorless crystals, m.p. 155 °C.—For isolation of *(3b)* the excess of benzylamine is evaporated at 120 °C/0.1 torr and the solid residue is recrystal-

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lized twice from *n*-heptane, giving colorless crystals, m.p. 220 °C (dec.) (yield 1.00 g, 30%).

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CAS Registry Numbers:
(1): 52195-97-8 / *(3a)*: 52195-98-9 / *(3b)*: 52195-99-0 / *(4)*: 52196-00-6 / *(5)*: 52196-01-7 / CH_3NH_2: 74-89-5 / $C_6H_5CH_2NH_2$: 100-46-9 / C_6H_5CN: 100-47-0; CS_2: 75-15-0 / C_6H_5NCS: 103-72-0.

[1] *B. A. Nevett* and *R. S. Tobias*, Chem. Ind. (London) *1963*, 40.
[2] *H. J. Götze*, Angew. Chem. *86*, 104 (1974); Angew. Chem. internat. Edit. *13*, 88 (1974).
[3] *K. Jones* and *F. Lappert*, J. Chem. Soc. *1965*, 1944.
[4] *H. Puff* and *R. Zimmer*, unpublished work.

Stereospecific Hydrogenations with Hydrogen Gas and Microorganisms as Catalysts[**]

By *Helmut Simon, Bernhard Rambeck, Hironobu Hashimoto, Helmut Günther, Gerhard Nohynek*, and *Helmut Neumann*[*]

There are numerous microorganisms that cause evolution of gaseous hydrogen[1], but there appears to have been no attempt hitherto to carry out hydrogenations with hydrogen gas and microorganisms by reversing the reaction chain that leads to formation of hydrogen. We have used *Clostridium kluyveri*[2] to hydrogenate numerous α,β-unsaturated carboxylic acids, and *Bacillus polymyxa* (NRC-9035)[3] to obtain diols from α-hydroxy ketones, or α-hydroxy ketones and diols from α-oxo acids.

Table 1 shows the relative rates of hydrogenation of, in each case, 0.1 mmol of unsaturated carboxylic acid by means of 80 mg (dry weight) of *Clostridium* in 3 ml of 0.1 M phosphate buffer (pH = 7.0) at 35 °C and 1 atm pressure of hydrogen gas. The absolute rate of hydrogenation amounts to *ca.* 40 μmol/h for tiglate. At 35 C such cells are active for 60–100 h in the presence of tetracycline. The compounds marked [a] in Table 1 were also hydrogenated on a 2 to 10 mmol scale. Insofar as the products were not new it was established that their hydrogenation was completely stereospecific.

This hydrogenation procedure enables one to obtain on a preparative scale a wide variety of compounds that are chiral only because of stereospecific replacement of H by D and/or T. The [2,3-D_2]-3-phenylpropionic acid obtained in a D_2O buffer has $[\alpha]_{365}^{25} = -7.0$ as sodium salt in water ($c = 0.076$ g/ml).

(3*S*)[3-D,3-T]Propionic acid can be prepared from *cis*-dideuterioacrylic acid[4] in HTO. This procedure is probably the simplest way of obtaining chiral methyl groups on a preparative scale.

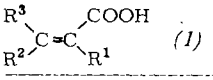
Pyruvate and acetoin are intermediates in the fermentation of D-glucose to (2*R*,3*R*)-butanediol by *Bacillus polymyxa*. In view of the overall equation:

$$3CH_3COCOOH + H_2O \rightarrow CH_3CHOHCHOHCH_3 + 3CO_2 + CH_3COOH$$

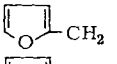
formation of 2,3-butanediol from pyruvate should also be possible. Pyruvate or 2-oxobutyrate in an atmosphere of nitrogen was, however, almost exclusively decarboxylated oxidatively, with evolution of hydrogen. Nevertheless, under 90 atm pressure of hydrogen the following reactions occur under catalysis by *B. polymyxa* (yields in parentheses):

Pyruvate	→	(2*R*,3*R*)-Butanediol	(65%)
(*R*,*S*)-Acetoin	→	*erythro*- and *threo*-Butanediol	(100%)
2-Hydroxy-3-pentanone	→	Pentanediol	(100%)
(*R*,*S*)-Propionin	→	*erythro*- and *threo*-Hexanediol	(60%)
2-Oxobutyrate	→	Hexanediol	(20%)

Table 1. Examples of acids *(1)* that were hydrogenated by *Clostridium kluyveri* and hydrogen gas.



(1)

Acid	R^1	R^2	R^3	V_{rel}
Tiglic acid	CH_3	CH_3	H	1.0
Angelic acid [a]	CH_3	H	CH_3	0.2
Acrylic acid	H	H	H	3.2
Methacrylic acid	CH_3	H	H	2.0
Dimethylacrylic acid	H	CH_3	CH_3	0.2
E-2-Pentenoic acid	H	C_2H_5	H	1.0
E-2-Hexenoic acid	H	*n*-C_3H_7	H	0.9
Sorbic acid	H	*n*-C_3H_5	H	1.0
Ethyl hydrogen fumarate	H	$C_3H_5O_2C$	H	0.6
E-3-Furfurylacrylic acid	H		H	1.0
E-3-(2-Thienyl)acrylic acid	H		H	1.3
Cinnamic acid [a]	H	C_6H_5	H	0.9
E-α-Methylcinnamic acid [a]	CH_3	C_6H_5	H	0.7
Z-*p*-Chloro-α-methoxycinnamic acid [a]	OCH_3	C_6H_4Cl	H	0.8
Z-*p*-Bromo-α-methoxycinnamic acid [a]	OCH_3	C_6H_4Br	H	0.8
1-Cyclohexenecarboxylic acid	$-(CH_2)_4-$		H	0.1

[a] See text.

For example, 11.0 g (100 mmol) of sodium pyruvate was incubated with 20 g (dry wt.) of *B. polymyxa* in 150 ml of 0.05 M phosphate buffer (pH = 6.7) in an autoclave for 25 h at 35 °C.

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tiglic acid: 80-59-1 / angelic acid: 565-63-9 / acrylic acid: 79-10-7 / methacrylic acid: 79-41-4 / dimethylacrylic acid: 541-47-9 / *E*-2-pentenoic acid: 13991-37-2 / *E*-2-hexenoic acid: 13419-69-7 / sorbic acid: 110-44-1 / monoethyl fumarate: 2459-05-4 / cinnamic acid: 621-82-9 / *E*-α-methylcinnamic acid: 1895-97-2 / *Z*-*p*-chloro-α-methoxycinnamic acid: 52217-00-2 / *Z*-*p*-bromo-α-methoxycinnamic acid: 52217-01-3 / 1-cyclohexenecarboxylic acid: 636-82-8 / sodium pyruvate: 113-24-6 / (*R*,*S*)-acetoin: 52217-02-4 / *erythro*-2,3-butanediol: 5341-95-7 / *threo*-

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2,3-butanediol: 35007-63-7 / 2-hydroxy-3-pentanone: 5704-20-1 / 2,3-pentanediol: 42027-23-6 / (*R,S*)-propionin: 52217-03-5 / *erythro*-3,4-hexanediol: 22520-39-4 / *threo*-3,4-hexanediol: 52217-04-6 / sodium 2-oxobutyrate: 2013-26-5 / 3,4-hexanediol: 922-17-8.

[1] *C. T. Gray* and *H. Gest*, Science *148*, 186 (1965).

[2] *H. U. Bergmeyer, G. Holz, H. Klotzsch*, and *G. Lang*, Biochem. Z. *388*, 114 (1963). We are grateful to Dr. *G. Holz* of the C. F. Boehringer company, Tutzing, for cell material for starting cultures.

[3] *H. Katznelson* and *A. G. Lochhead*, Can. J. Res. *22C*, 273 (1944); *G. A. Adams* and *J. D. Leslie*, *ibid. 24F*, 107 (1946).

[4] *R. K. Hill* and *G. R. Newkome*, J. Org. Chem. *34*, 740 (1969).

Stereospecific Hydrogenation of (*R*)- or (*S*)-2-Ethyl-4-phenylallenecarboxylic Acid to *cis*- or *trans*-2-Ethyl-4-phenyl-3-butenecarboxylic Acid by Means of *Clostridium kluyveri*

By *Bernhard Rambeck* and *Helmut Simon*[*]

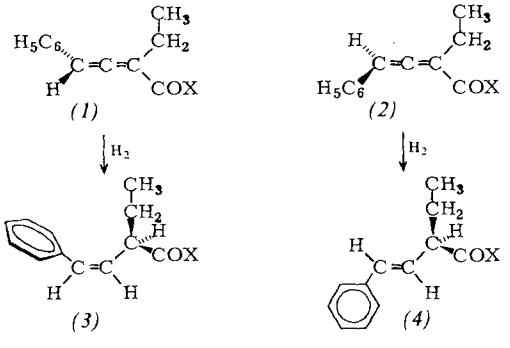
Hydrogenation with hydrogen gas and microorganisms described in[1] can be effected also for 2,4-disubstituted allenecarboxylic acids[2] such as 4-ethyl-2-methyl-, 2-ethyl-4-methyl-, and 2-ethyl-4-phenyl-allenecarboxylic acid. This was studied in detail for (*R*)- and (*S*)-2-ethyl-4-phenylallenecarboxylic acid (2-ethyl-4-phenyl-2,3-butadienoic acids) *(1)* and *(2)*.

Enzymic reactions of enantiomeric molecules not possessing a center of asymmetry have hitherto been investigated hardly at all. If 1.0 mmol of the racemate *(1)*/*(2)* as sodium salt is shaken with 1.2 g (dry weight) of *C. kluyveri* in 25 ml of 0.1 M phosphate buffer (pH = 7.0) at 35 °C under 1 atm of hydrogen gas, two products, *(3)* and *(4)*, are formed, quantitatively and in equal amounts. Hydrogenation of *(1)* and *(2)* in separate experiments proceeds equally fast. The structures *(3)* and *(4)* can be deduced from the results shown in Table 1 together with the fact that hydrogenation of *(4)* or of a 1:1 mixture of *(3)* and *(4)* by chlorotris(triphenylphosphane)rhodium affords the same optically active product. The rotations of the sodium salts of the hydrogenation products *(3)* and *(4)* in water ($c = 0.0038$ and 0.0058, respectively) amount to $[\alpha]_D^{25} = -31°$ and $-29°$, respectively. The optical activity is greatly increased by the chiral twisting of the π-system of *(3)*: at 350 nm the specific rotation is almost $-2500°$.

Whether *(3)* and *(4)* exist in the *R*- or the *S*-configuration cannot yet be stated with certainty: neither *(3)* nor *(4)* has been described in the literature. However, the *R*-configuration appears very probable. For several derivatives of 2-methyl-carboxylic acids, such as 2-methyl-3-butenoate, 2-methylbutyrate, and 2-methyl-3-phenylpropionate, the compound with the negative rotation always has the *R*-configuration. For the first two of these compounds transition from the sodium salt in water to the free acid in chloroform shifts the rotation to more negative values, and this occurs also for *(3)* and *(4)* (cf. Table 1). Since *(1)* gives the *cis*-compound *(3)* whilst *(2)* gives the *trans*-compound *(4)*, and with the assumption that *(3)* and *(4)* have the *R*-configuration, the addition of hydrogen is seen to occur *trans*. This is in accord with the *trans*-addition by means of butyryl-CoA-dehydrogenase[4]. What is surprising is that the two enantiomers are formed at equal rates, particularly in view of the sterically very unfavorable *cis*-configuration of *(3)*.

Table 1. Some data for the products obtained on hydrogenation of *(1)* and *(2)* or the racemate *(1)*/*(2)*.

	(3) from *(1)*	*(4)* from *(2)*	*(3)* and *(4)* from *(1)*/*(2)*
UV (Na salt in D_2O) λ_{max} (ε)	245 nm (7000)	255 nm (14100)	250 nm (10500)
Retention time on high-pressure chromatography based on *(1)*/*(2)*	0.6	1.0	0.6 and 1.0
$[\alpha]_D^{25}$ of the Na salt ($c = 0.038$ g/ml in D_2O)	−215	+ 7	−115
$[\alpha]_D^{25}$ of the free acid ($c = 0.014$ g/ml of $CHCl_3$)	−450	−66	−225
Coupling constant J of the vinylic protons in the NMR spectrum	12 Hz	15 Hz	



X = OH or (thioester with coenzyme A)

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CAS Registry Numbers:
(1): 52216-94-1 / *(2)*: 52340-23-5 / racemate *(1)* / *(2)*: 52248-51-8 / *(3)*: 52216-95-2 / *(3)* (Na salt): 52216-96-3 / *(4)*: 52216-97-4 / *(4)* (Na salt): 52216-98-5.

[1] *H. Simon, B. Rambeck, H. Hashimoto, H. Günther, G. Nohynek*, and *H. Neumann*, Angew. Chem. *86*, 675 (1974); Angew. Chem. internat. Edit. *13*, 608 (1974).

[2] We thank Prof. *G. Kresze* and Dr. *W. Runge* for discussions and for the gift of allenecarboxylic acid (synthesis as in [3]).

[3] *G. Kresze, W. Runge*, and *E. Ruch*, Liebigs Ann. Chem. *756*, 112 (1972); *G. Kresze* and *W. Runge*, unpublished work.

[4] *H. J. LaRoche, M. Kellner, H. Günther*, and *H. Simon*, Hoppe-Seylers Z. Physiol. Chem. *352*, 399 (1971).

Transition Metal-Carbon Triple Bonds[**]

By *Gottfried Huttner, Hans Lorenz*, and *Wolfgang Gartzke*[*]

E. O. Fischer et al.[1] recently reported a new type of transition metal complex of composition $(CO)_4(Hal)MCR$ and $(CO)_3[P(CH_3)_3](Hal)MCR$ (M = Cr, Mo or W; Hal = Cl, Br or I; R = CH_3, C_6H_5 or C_6H_4R'); their properties indicated

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a completely novel type of bond between an sp-hybridized carbon atom and a transition-metal atom. In order to prove conclusively the metal-carbon triple bond postulated from valence-electronic considerations and thus the structures proposed for these complexes, we have carried out complete, three-dimensional X-ray structure analyses for $(CO)_4(I)WCC_6H_5$ *(1)*, $(CO)_4(I)CrCCH_3$ *(2)*, and $(CO)_3[P(CH_3)_3](Br)CrCCH_3$ *(3)*[1a].

Table 1. Crystallographic data for *trans*-haloalkyl(aryl)carbyne complexes *(1)* to *(3)*. The figures in parentheses denote standard deviations in units of the last decimal.

	(1)	*(2)*	*(3)*
a [pm]	2010(2)	791.1(9)	683.5(8)
b [pm]	1212(1)	1179.5(10)	1366.7(10)
c [pm]	1126(1)	1074.7(10)	1426.1(10)
α [ ]	90	90	90
β [ ]	90	90	96.55(7)
γ [ ]	90	90	90
V [pm^3]	2744(9)·10^6	1003(3)·10^6	1332(4)·10^6
d [gcm^{-3}]	2.478(9)	2.106(8)	1.758(8)
Space group	Pbca	Cmcm	$P2_1$
Z	8	4	4

Reflection data were collected on a Weissenberg diffractometer in the region $0 < \sin\vartheta/\lambda \leq 0.6$ ($Mo_{K\alpha}$ radiation, $\lambda = 71.069$ pm), compounds *(2)* and *(3)* being cooled to the temperature -40 ± 5 C. After Lorentz, polarization, and absorption corrections of the measured intensities all three structures were solved by conventional Patterson and difference-Fourier methods. Partial [for *(1)* and *(3)*] or complete anisotropic [for *(2)*] refinement led to R factors of 0.078 for *(1)* [688 reflections], 0.05 for *(2)* [425 reflections], and 0.07 for *(3)* [1128 reflections].

All three complexes have a slightly distorted pseudooctahedral configuration (Figs. 1—3). In all cases the halogen atom occupies a position *trans* to the "carbyne" group.

$(CO)_4(I)WCC_6H_5$ *(1)* has four equatorial carbonyl groups with W—C_{CO} separations of 207(6) pm (mean value), which correspond to the length of the W—C_{CO} bond in $W(CO)_6$ [205.8 pm][2]. Some of the W—C—O groups appear not to be linear. The W—I separation, at 284.5(5) pm is not unusual in comparison with the sum of the covalent radii of iodine (140 pm) and tungsten (135 pm)[3]. The W—$C_{carbyne}$ separation [190(5) pm] is shorter than the W—C_{CO} bonds and is thus the shortest tungsten-carbon separation found so far in organometallic compounds. The W—C—R group is not linear, as might be expected for an sp-hybridized carbon atom. The plane of the W—C—R angle [162(4)°] is almost perpendicular to that of the phenyl ring.

The molecule $(CO)_4(I)CrCCH_3$ *(2)* possesses two mutually perpendicular mirror planes; the atoms I, Cr, $C_{carbyne}$, and C_{methyl} lie on their line of intersection. Because of this symmetry, only one independent Cr—C_{CO} distance could be determined [194.6(9) pm]. The length of the Cr—I bond at 279.2(2) pm is close to the sum of the covalent radii of chromium and iodine[3]. The Cr—$C_{carbyne}$ bond length [169(1) pm] is the shortest Cr—C distance known so far (cf. Table 2).

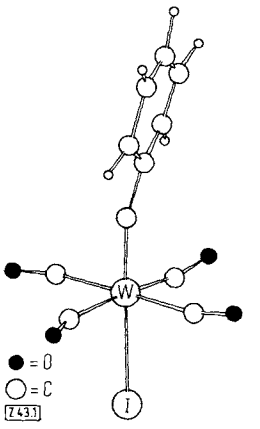


Fig. 1. Molecular structure of $(CO)_4(I)WCC_6H_5$ *(1)*.

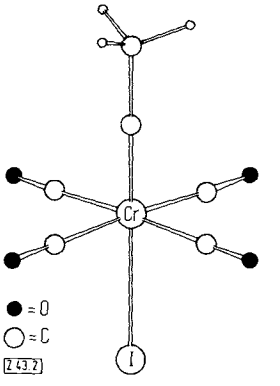


Fig. 2. Molecular structure of $(CO)_4(I)CrCCH_3$ *(2)*.

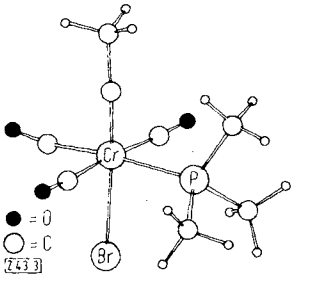


Fig. 3. Molecular structure of $(CO)_3[P(CH_3)_3](Br)CrCCH_3$ *(3)*.

Table 2. Metal-carbon separations in organometallic compounds involving various bond orders. Figures in parentheses denote standard deviations in units of the last decimal.

	σ-Single bonds		"Double bonds" (carbene and carbonyl)		Triple bonds (carbyne)	
	Compound	Separation [pm]	Compound	Separation [pm]	Compound	Separation [pm]
Chromium	$[(o\text{-}CH_3OC_6H_4)_2(bipy)_2Cr]I$ [5]	210(1) [a]	$(CO)_5CrC(OCH_3)C_6H_5$ [10]	204(3)	*(2)*	169(1)
	$(p\text{-}CH_3C_6H_4)CrCl_2 \cdot 3THF$ [6]	201.4(10) [a]	$(CO)_5CrC(NHCH_3)CH_3$ [10]	209(2)	*(3)*	168(3)
	$Li_4Cr_2(CH_3)_8 \cdot 4THF$ [7]	219.9(13)	$(CO)_5CrC(N(CH_3)_2)OC_2H_5$ [10]	213.3(4)		
	$Li_4Cr_2(C_4H_8)_4 \cdot 4THF$ [8]	223.8(22)	$(CO)_5CrC(N(C_2H_5)_2)CH_3$ [10]	216(1)		
			Cr—C_{CO} in $Cr(CO)_6$ [11]	190.9(3)		
Tungsten	$\pi\text{-}C_5H_5(CO)_3WC_6H_5$ [9]	232	W—$C_{Carbene}$	unknown	*(1)*	190(5)
			W—C_{CO} in $W(CO)_6$ [2]	205.8(3)		

[a] Shortened by a π-bonding contribution.

The methyl group is connected to the carbyne-carbon by a normal single bond [149(2) pm]. The Cr—C—CH_3 arrangement appears to be linear, even though F_c calculations with disordered bent molecular models show no influence on the R factor provided that the angular deviation does not exceed 5°.

$(CO)_3[P(CH_3)_3](Br)CrCCH_3$ *(3)* crystallizes with two crystallographically independent molecules in the asymmetric unit of the cell. Both independent molecules have identical geometries within experimental error. Mean values of the bond lengths are: Cr—C_{CO} 193(4), Cr—Br 260.3(5), Cr—P 239.6(9) pm. The Cr—$C_{carbyne}$ separation [168(3) pm] is almost identical with that in *(2)*. The deviation of the Cr—C—CH_3 group from linearity is not significant [177(3)°].

Table 2 shows some bond lengths for chromium and tungsten complexes with metal-carbon single bonds, metal-carbene bonds which can be regarded as partial double bonds, and the new metal-carbyne bonds.

The metal-carbyne carbon bonds are shorter by *ca.* 40 pm than a metal-carbon single bond in the case of tungsten and by *ca.* 50 pm in the case of chromium. For comparison, the shortening in the series alkane, alkene and alkyne is 33 pm (ethane 154, ethylene 134, acetylene 121 pm)[4]. The extremely short metal-carbon separation in the compounds of this study supports the proposition of a metal-carbon triple bond.

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CAS Registry Numbers:
(1): 50726-28-8 / *(2)*: 50701-14-9 / *(3)*: 52175-60-7.

[1] *E. O. Fischer, G. Kreis, C. G. Kreiter, J. Müller, G. Huttner*, and *H. Lorenz*, Angew. Chem. *85*, 618 (1973); Angew. Chem. internat. Edit. *12*, 564 (1973).

[1a] We thank Dr. *G. Kreis* and Dipl.-Chem. *K. Richter* for the preparation of single crystals.

[2] *S. P. Arnesen* and *H. M. Seip*, Acta Chem. Scand. *20*, 2711 (1966).

[3] *J. C. Slater*, J. Chem. Phys. *41*, 3199 (1964).

[4] *B. P. Stoicheff*, Tetrahedron *17*, 135 (1962).

[5] *J. J. Daly, F. Sanz, R. P. A. Sneeden*, and *H. H. Zeiss*, Chem. Commun. *1971*, 243.

[6] *J. J. Daly* and *R. P. A. Sneeden*, J. Chem. Soc. *A 1967*, 736.

[7] *J. Krausse, G. Marx*, and *G. Schödl*, J. Organometal. Chem. *21*, 159 (1970).

[8] *J. Krausse* and *G. Schödl*, J. Organometal. Chem. *27*, 59 (1971).

[9] *V. A. Semion* and *Y. T. Struchkov*, Zh. Strukt. Khim. *9*, 1046 (1968).

[10] Cf. *G. Huttner* and *B. Krieg*, Chem. Ber. *105*, 67 (1972).

[11] *A. Whitaker* and *J. W. Jeffery*, Acta Crystallogr. *23*, 977 (1967).

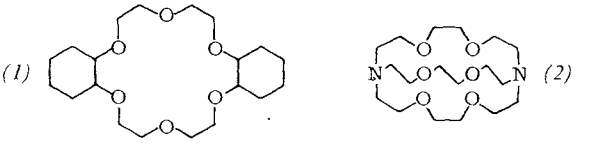
Dissolution of Alkali Metals in Aromatic Hydrocarbon Solvents by Cryptate Formation

By *Bernd Kaempf, Serge Raynal, André Collet, François Schué, Sylvie Boileau*, and *Jean-Marie Lehn*[*]

Macrocyclic and macrobicyclic ligands such as *(1)* and *(2)*, which form stable complexes with alkali metal cations, may be used for dissolving alkali metals in amines or ethers[1-3]. Crown ethers like *(1)* give blue solutions containing mainly the metal anion $M^{\ominus}$ as counter ion of the cation complex. Formation of the more stable alkali cryptate complexes of *(2)* displaces the equilibria towards the generation of solvated electrons[3]. Yellow to red solutions, showing an ESR signal, are obtained when polyethylene oxide in benzene is brought in contact with Na/K alloy. Faintly colored solutions were also obtained with the same system in presence of aromatic hydrocarbons[4].

We wish to report the dissolution of alkali metals in benzene and toluene in presence of *(1)* and *(2)* and some data on the properties of such solutions. All the experiments described employed vacuum line techniques.

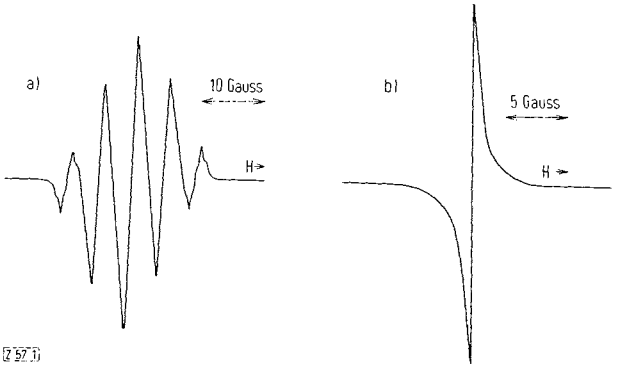
When the macrobicyclic cryptand *(2)* (about 15 mg) is added to benzene (about 10 ml) in contact with a film of potassium metal, the film is attacked and dissolves slowly yielding a dark blue solution. Similar results are obtained when potas-



sium is replaced by sodium and/or benzene by toluene. When the macrocyclic crown ether *(1)* is used in place of *(2)*, potassium is also found to dissolve in benzene or toluene. Various other solutions of sodium, potassium, rubidium, or cesium in benzene, toluene, as well as in tetrahydrofuran (see also [1,3]) or tetrahydropyran, have been obtained using *(2)* or other suitable cryptands[5] which form stable complexes with the corresponding cations.

The ESR spectra at −70 °C of the K/*(1)*/benzene or toluene solutions display an intense multiplet with broadened lines. The observed spectra correspond respectively to the radical anion of benzene (seven lines; $a_H \approx 3.8$ G) and of toluene (five lines; see Fig. 1a). In the presence of *(2)* the same systems give an intense single line (see Fig. 1b). In no case was coupling to the metal cation observed.

These results may be interpreted as follows. Dissolution of potassium in benzene or toluene is due to the formation of the stable crown and cryptate complexes of the metal cation. The electron is transferred to a solvent molecule giving a radical anion. When the ligand is a macrocycle like *(1)*, the complexed cation may still be approached by the anion from the top or bottom of the [$K^{\oplus}$, *(1)*] disk, forming a (complexed cation)—(radical anion) ion pair in solvents of



[Z 57 I]

Fig. 1. ESR spectrum at −70 °C of the solution obtained by dissolving a film of potassium metal in toluene using a) the macrocyclic ligand *(1)*, b) the macrobicyclic ligand *(2)*.

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low dielectric constant (for a similar pairing with fluorenyl anion, see ref. [6]). The ESR spectrum of potassium naphthalenide in THF displays a very broad signal and a sharp signal, which have been attributed to the coexistence, respectively, of ion pairs undergoing slow electron exchange and free anions with fast electron exchange[7]. Thus the observation of hyperfine structure in the ESR spectra of solutions containing ligand *(1)* indicates that one is indeed dealing with ion pairs undergoing slow electron exchange.

When the ligand is *(2)*, the complexed cation is well hidden inside the three-dimensional molecular cavity so that in effect a sodium or potassium cation is transformed into a very bulky cryptate cation of about 5 Å radius (ionic radius of $Cs^{\oplus} \approx 1.65$ Å). Thus cation-anion interactions are weak and the radical anion is a much less stable, free or weakly paired anion. Consequently the electron transfer reaction is expected to be fast[7] and the radical anion multiplet collapses into a single ESR line.

The UV spectrum of K/*(1)*/benzene contains bands at about 300 and 435 nm, similar to those ascribed to the benzene radical anion in dimethoxyethane (DME) at −70 °C[8]. The spectrum of K/*(2)*/benzene displays only the 435 nm band; the other band might be obscured by the solvent band.

Very intense ESR spectra have been observed for K/*(2)*/toluene solutions on addition of biphenyl, naphthalene, or anthracene. The K/*(2)*/biphenyl system in toluene displays an intense, "exchange-narrowed" single ESR line (about 1.5 G wide) from −70 °C to +38 °C, while the spectrum of the biphenyl radical anion in DME is a complex multiplet extending over about 20 G[9]. The UV spectrum of the solution contains bands at about 400 and 630 nm (intensity ratio 3:1) similar to those reported for the biphenyl radical anion in THF[10]. Although naphthalene-sodium is not soluble in benzene[11], addition of naphthalene to K/*(2)*/toluene immediately produces the characteristic green solution of the naphthalene radical anion. The ESR spectrum at −20 °C is a broad line with some remaining, broadened fine structure, indicating moderately fast electron exchange. Other species, like diamagnetic dianions, may be present to some extent in the solutions described here in addition to the paramagnetic radical anions.

The alkali metal solutions with cryptands *(2)* may present interesting properties and applications in organic chemistry, for instance as reducing agents. Because of the low electron affinity of benzene or toluene and of the weak interactions with the bulky cation, enhanced reducing properties may be expected. It has already been shown that these solutions are efficient initiators for anionic polymerization of various monomers[12].

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CAS Registry Numbers:
[K⁺, *(1)*]: 31270-18-5 / [K⁺, *(2)*]: 32611-95-3 / toluene radical anion: 34509-95-0.

[1] *M. T. Lok, F. J. Tehan*, and *J. L. Dye*, J. Phys. Chem. *76*, 2975 (1972).

[2] *J. L. Dye, M. G. DeBacker*, and *V. A. Nicely*, J. Amer. Chem. Soc. *92*, 5226 (1970).

[3] *J. L. Dye, M. T. Lok, F. J. Tehan, R. B. Coolen, N. Papadakis, J. M. Ceraso*, and *M. G. DeBaker*, Ber. Bunsenges. Phys. Chem. *75*, 659 (1971).

[4] *I. M. Panayotov, Ch. B. Tsvetanov, I. V. Berlinova*, and *R. S. Velichkova*, Makromol. Chem. *134*, 313 (1970).

[5] *B. Dietrich, J. M. Lehn, J. P. Sauvage*, and *J. Blanzat*, Tetrahedron *29*, 1629 (1973); *B. Dietrich, J. M. Lehn*, and *J. P. Sauvage*, *ibid.* *29*, 1647 (1973); *J. M. Lehn*, Struct. Bonding *16*, 1 (1973).

[6] *J. Smid*, Angew. Chem. *84*, 127 (1972); Angew. Chem. internat. Edit. *11*, 112 (1972), and references therein.

[7] *R. Chang* and *C. S. Johnson, Jr.*, J. Amer. Chem. Soc. *88*, 2338 (1966).

[8] *C. L. Gardner*, J. Chem. Phys. *45*, 572 (1966).

[9] *H. Nishiguchi, Y. Nakai, K. Nakamura, K. Ishizu, Y. Deguchi*, and *H. Takaki*, J. Chem. Phys. *40*, 241 (1964).

[10] *M. Szwarc*: Carbanions, Living Polymers, Interscience, New York 1968.

[11] *M. Szwarc*, Makromol. Chem. *35*, 132 (1960).

[12] *S. Boileau, B. Kaempf, J. M. Lehn*, and *F. Schué*, J. Polym. Sci., Polym. Lett. *12*, 203 (1974); *S. Boileau, B. Kaempf, S. Raynal, J. Lacoste*, and *F. Schué*, J. Polym. Sci., Polym. Lett. *12*, 211 (1974).

Structure of Xenon Hexafluoride in Solution: Xe_4F_{24}

By *Herbert Rupp* and *Konrad Seppelt*[*]

The structure of xenon hexafluoride in the solid state has already been determined: the crystal contains tetrameric and hexameric units $[XeF_5^+ F^-]_n$[1]. There are still doubts, however, about the structure of monomeric XeF_6 in the gaseous state—three rapidly interconvertible electronic isomers are under discussion[2]. So far very little has been reported about the structure of XeF_6 in the liquid or dissolved state. We have now investigated this problem by means of ^{19}F- and ^{129}Xe-NMR spectroscopy.

Difficulties were encountered in choosing a suitable solvent; it should be resistant to attack by XeF_6, have high dissolving power, low polarity and low melting point, and favor neither formation of fluorine bridges nor intermolecular fluorine exchange (as *e.g.* HF or BrF_5). It was found that bis(pentafluorosulfur) oxide, $(F_5S)_2O$ (m.p. −115, b.p. 31 °C[3]) satisfies all these requirements.

Xenon hexafluoride dissolves in $(F_5S)_2O$ at room temperature to give a yellowish green solution, thus indicating the presence of monomeric XeF_6 which is also yellowish green in the gaseous state. The ^{19}F- and ^{129}Xe-NMR spectra each show one broad signal ($\delta_F = -118.3$ ppm relative to $CFCl_3$[4], line width ≈200 Hz; $\delta_{Xe} = -5296$ ppm relative to xenon gas[4], dissolved in CF_2Cl_2, line width ≈70 Hz). On lowering the temperature to −45 °C the solution becomes colorless and both spectra are now found to contain sharper signals, in each case shifted slightly upfield ($\delta_F = -109.3$ ppm, line width ≈20 Hz; $\delta_{Xe} = -5292$ ppm, line width ≈40 Hz). Aggregation of monomeric XeF_6 occurs and is complete at −45 °C. At room temperature an equilibrium exists between monomeric and

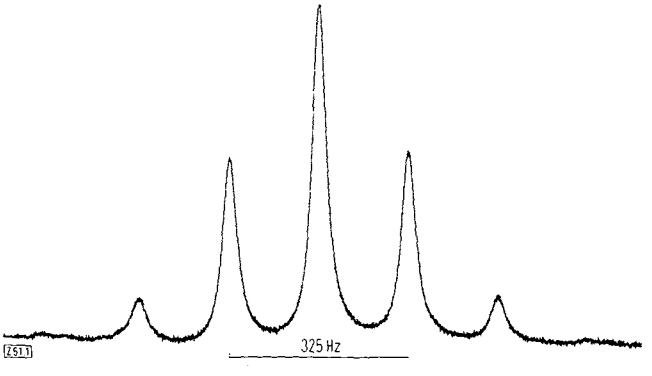


Fig. 1. ^{19}F-NMR spectrum of xenon hexafluoride in $(F_5S)_2O$ at −118 °C.

polymeric species. On lowering the temperature further, both types of NMR signals broaden again without change in the chemical shift, a coalescene point being reached at −75 °C. We interpret these findings in terms of intermolecular fluorine

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exchange being frozen. At the lowest possible temperature (−118 °C), the multiplets shown in Figures 1 and 2 are observed.

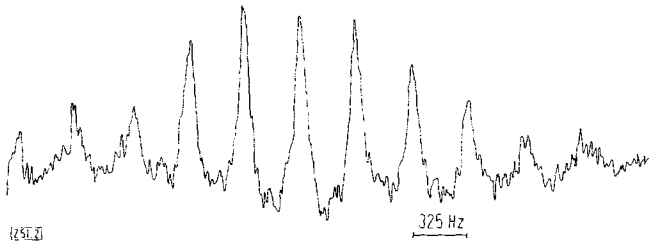


Fig. 2. ^{129}Xe-NMR spectrum of xenon hexafluoride in $(F_5S)_2O$ at −118 °C.

The seven equidistant lines (relative intensities 1.1 : 12.3 : 54.0 : 100 : 55.0 : 12.8 : 1.0) in the ^{19}F-NMR spectrum (Fig. 1) demonstrate that all fluorine atoms are magnetically as well as chemically equivalent. They couple with four equivalent xenon atoms ($J_{^{129}Xe-F} = 325 \pm 3$ Hz). Considering the natural abundance of ^{129}Xe (26.24%, nuclear spin 1/2), one would expect a nine-line spectrum (0.05 : 1.4 : 12.7 : 53.8 : 100 : 53.8 : 12.7 : 1.4 : 0.05). Coupling with ^{131}Xe (nuclear spin 3/2) is not observed because of quadrupole relaxation.

If each fluorine atom couples simultaneously with 4 xenon atoms, then each xenon atom necessarily couples with 24 fluorine atoms(!). Hence the ^{129}Xe-NMR spectrum ought to contain a multiplet of 25 lines, whose relative intensities are given by a binomial distribution of the 24th order. Despite the poor solubility of the compound at such low temperatures, the relatively small isotopic abundance of ^{129}Xe, the moderate specific sensitivity of this nuclear resonance, and the distribution of intensity over so many multiplet lines, a spectrum could still be recorded using the FT technique (Fig. 2). However, only 11–13 equidistant lines of the multiplet were recorded ($J_{Xe-F} = 325 \pm 5$ Hz); measurement of additional lines would have been too time consuming. Thus the intensity of the 6th and 20th line is already as low as 0.3 relative to that of the central 13th line (= 100), while the relative intensity of the 1st and 25th line is only 3.7×10^{-5}. It follows from the intensity distribution that we are dealing with a spectrum of odd multiplicity greater than 19 or 21.

We therefore come to the conclusion that xenon hexafluoride is present in the tetrameric form in solution at −118 °C and that all the xenon atoms and all the fluorine atoms are equivalent. Several structures are conceivable in which the xenon atoms are arranged tetrahedrally. All molecular models demand that intramolecular fluorine exchange occurs within the NMR time-scale, for each fluorine atom "sees" four equal xenon atoms, and each xenon atom 24 equal fluorine atoms. Xe_4F_{24} is thus an extreme—to our knowledge the most extreme—example of a non-rigid molecule.

Bonding between the Xe atoms could be effected by the orbitals not used in Xe—F bonds. Possibly there is a three-center two-electron bond situated on each tetrahedral face. The xenon atoms would then be ninefold coordinated (sp^3d^5) (Fig. 3a). Intramolecular fluorine exchange would be possible *via* the tetrahedral faces (Fig. 3b). This proposed structure resembles

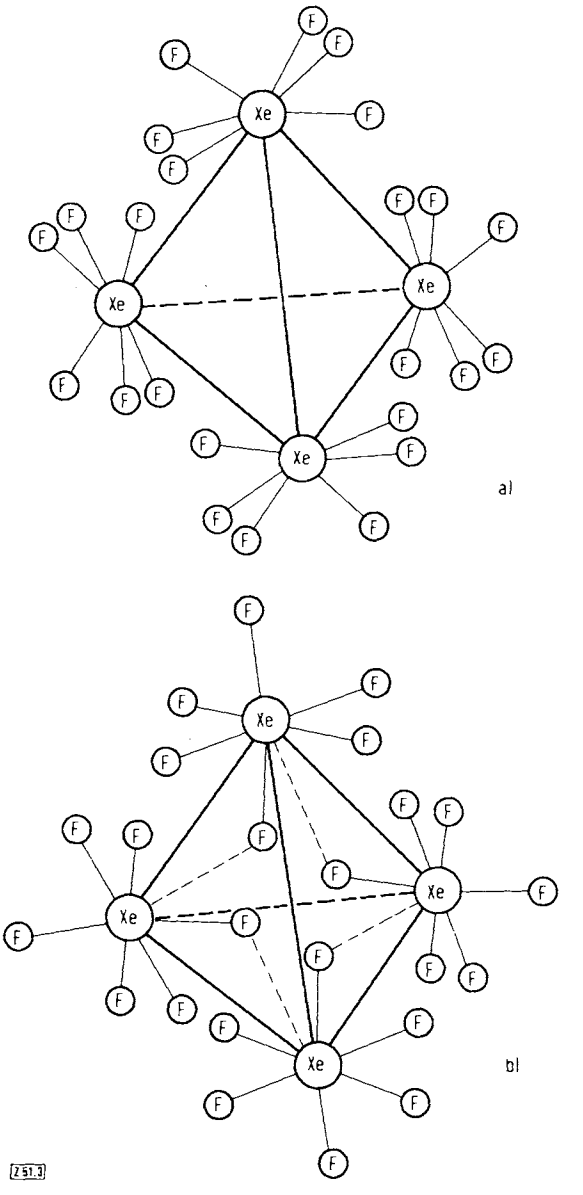


Fig. 3. Two possible structures of Xe_4F_{24} in solution.

in part the structure of crystalline xenon hexafluoride[1]. Fluorine exchange within the Xe_4F_{24} molecule can be regarded as simultaneous pseudorotation of all fluorine atoms (cog-wheel mechanism).

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[1] *R. D. Burbank* and *G. R. Jones*, Science *168*, 248 (1970); *P. A. Agron, C. K. Johnson*, and *H. A. Levy*, Inorg. Nucl. Chem. Lett. *1*, 145 (1965).

[2] *H. H. Claassen, G. L. Goodman*, and *H. Kim*, J. Chem. Phys. *56*, 5042 (1972); *G. L. Goodman, ibid. 56*, 5038 (1972).

[3] *H. L. Roberts*, J. Chem. Soc. *1960*, 2774.

[4] Negative sign denotes downfield shift (to higher frequency).

Reviews

Abstracts of selected progress reports and review articles

The higher oxidation states of iron, cobalt, and nickel are reviewed by *W. Levason* and *C. A. McAuliffe*. For iron, the (formal) oxidation states 4—6, for cobalt 3 (only partially) to 5, and for nickel, 3 and 4 are covered. Some halides, oxides, and oxo compounds have been known for a long time; recently, more and more complexes have been found where the higher oxidation states are stabilized by coordination, especially with sulfur, phosphorus, and arsenic donor ligands. In a chapter entitled "oxidation states and bonding", the difficulties of elucidating the true electron distribution in such compounds are stressed. [Higher Oxidation State Chemistry of Iron, Cobalt, and Nickel. Coord. Chem. Rev. *12*, 151—184 (1974); 398 references]

[Rd 716 IE—H]

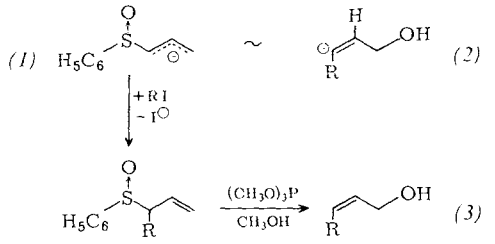
The stability of fluoride complexes in aqueous solutions is correlated with the sizes and charges of the metal ions by *G. Hefter*. Strong anomalies in the case of complexes of elements in the lower right hand side of the periodic system (Hg^{2+}, Pb^{2+}, Sn^{2+}, Sb^{3+}, Bi^{3+}) are rationalized partially by the fact that d and f orbitals shield the nuclear charge less efficiently than s and p orbitals. Major inexplicable deviations from the electrostatic correlation lead the author to the opinion that some published stability constants might be in error. Enthalpies of complex formation seem to be independent of metal ion charge densities, whereas there is some indication of correlation with entropies of complex formation. [Simple Electrostatic Correlations of Fluoride Complexes in Aqueous Solutions. Coord. Chem. Rev. *12*, 221—239 (1974); 74 references]

[Rd 717 IE—H]

To what extent does perchlorate play the role of a ligand in solution? This question is discussed in a review by *L. Johansson*. Association of kinetically labile hydrated metal ions with perchlorate is insignificant, so that corrections for it are unimportant in equilibrium studies of their strong complexes, where perchlorates are used to maintain constant ionic strength. On the other hand, *e.g.*, Tl^+ forms a stronger complex with ClO_4^- than with F^-, and kinetically inert complex ions, such as cobaltammines, show comparatively stable perchlorate complexes. There is no obvious simple connection between the charge density on a metal ion and its affinity to the perchlorate ion. [The Role of the Perchlorate Ion as Ligand in Solution. Coord. Chem. Rev. *12*, 241—261 (1974); 88 references]

[Rd 718 IE—H]

Allylic sulfoxides—useful intermediates in organic chemistry—are reviewed in an article by *D. A. Evans* and *G. C. Andrews*. In allyl sulfoxides the chemical reactivity has reversed polarity. For example, the sulfoxide stabilized carbanion *(1)* can be regarded as the reversed polarity equivalent of the carbanion *(2)*. Ions of type *(1)* can be converted, *inter alia*, into open chain and cyclic compounds and regioselectively alkylated. Possible applications for the synthesis of cyclic compounds are outlined. [Allylic Sulfoxides: Useful Intermediates in Organic Synthesis. Accounts Chem. Res. 7, 147—155 (1974); 43 references]



[Rd 719 IE—L]

The base-catalyzed addition of hydrocarbons is reported on by *H. Pines*. Such additions are of synthetic interest because they afford hydrocarbons and related compounds by a simple one-step procedure. Hydrocarbons having a benzylic or allylic hydrogen atom are readily converted into carbanions on reaction with bases. These carbanions *e.g. (1)*, can add to olefinic hydrocarbons:

$$\underset{(1)}{C_6H_5CH^{\ominus}Na^{\oplus}} + CH_2{=}CH_2 \rightleftharpoons C_6H_5CH_2{-}CH_2{-}CH^{\ominus}Na^{\oplus}$$

$$C_6H_5CH_2{-}CH_2{-}CH^{\ominus}Na^{\oplus} + C_6H_5CH_3 \rightarrow C_6H_5CH_2CH_2{-}CH_3 + C_6H_5CH^{\ominus}Na^{\oplus}$$

Examples of their uses are the oligomerization of olefins, the addition of alkylarenes or alkylpyridines to olefins, intramolecular cyclizations and the addition of "aprotonic solvents", such as *N*-methyl-2-pyrrolidone, to olefins. [Base-Catalyzed Carbon-Carbon Addition of Hydrocarbons and of Related Compounds. Accounts Chem. Res. 7, 155—162 (1974); 64 references]

[Rd 720 IE—L]

The interaction of proteins with small molecules or ions such as O_2, ATP, amino acids, K^+ or Cu^{2+} has been studied by *I. M. Klotz* with special consideration being given to the stoichiometric and energetic aspects. The distribution of a ligand between solvent and protein in best described in terms of stepwise stoichiometric equilibria. It is shown how an affinity profile, which reveals the nature of the interaction, can be plotted from the measured values. [Protein Interactions with Small Molecules. Accounts Chem. Res. 7, 162—168 (1974); 37 references]

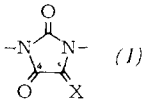
[Rd 721 IE—L]

Patents

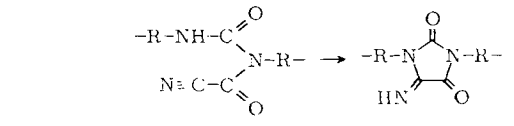
Abstracts of selected "Deutsche Offenlegungsschriften" (DOS), *i.e.* provisionally published specifications as filed with the German Patent Office

New heterocyclic polymers contain repeat units of disubstituted 1,3-imidazolidine-1,3-diyl rings having the formula *(1)*. X is NH, NR, or O, and may be situated on C-4 or C-5. The polymers are prepared by reaction of diisocyanates with hydro-

gen cyanide. Tertiary nitrogen bases are used as catalysts. Aromatic diisocyanates such as toluene diisocyanate are more reactive than the aliphatic analogs. Strongly polar, aprotic solvents such as DMSO, HMPT, and dimethylacetamide are suitable. The reaction proceeds in three steps at 6—10 °C. The polymer powder isolated can be made into insoluble,



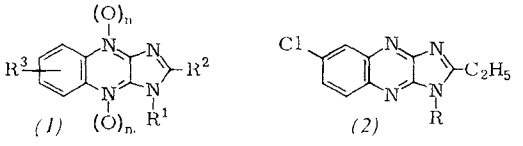
(1)



flexible films. [DOS 2113488; Esso Research and Engineering Co., Linden, N. J. (USA)]

[PR 196 IE—W]

Imidazo[4,5-*b*]quinoxalines having the general formula *(1)* and their salts with alkalis and mineral acids are new systemic



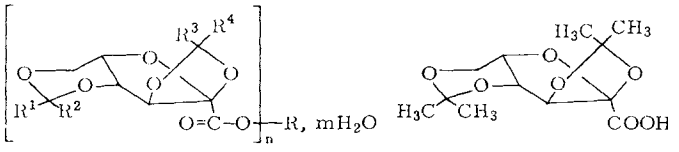
(1) *(2)*

R^1 = H, alkyl, alkoxycarbonylmethyl, carboxymethyl, benzyl, acyl, *etc.*; R^2 = alkyl ($< C_5$) or cyclopropyl; R^3 = H, halogen; n = 0,1; R = H, C_4H_9CO, $C_5H_{11}CO$, cyclopropanecarbonyl, CH_3OCO

fungicides for use against mildew fungi. The compounds *(2)* are particularly effective. [DOS 2339012; du Pont de Nemours and Co., Wilmington, Del. (USA)]

[PR 204 IE—S]

New growth regulators for plants are derivatives of L-sorbose having the general formula *(1)*, in particular the acid *(2)* and its salts and esters. They act preferentially in the post-ger-



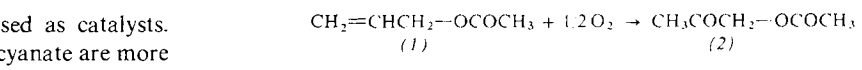
(1) *(2)*

n = 1, 2; m = 0, 1; R = H, metal ion, (subst.) ammonium ion or residue of a (subst.) aliphatic or cycloaliphatic alcohol; R^1—R^4 = H, alkyl, aryl

mination period as growth inhibitors, *e.g.* for grasses, ornamental plants, and shrubs, but can also be used to influence flowering and as herbicides. [DOS 2339239; F. Hoffmann-La Roche & Co. AG, Basel (Switzerland)]

[PR 205 IE—S]

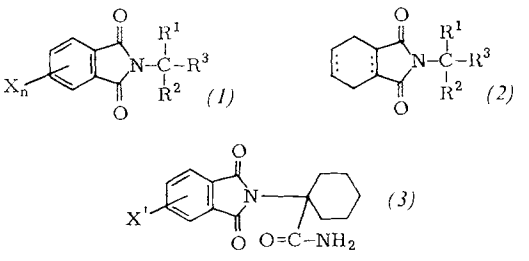
Acetonyl acetate ("acetoxyacetone") *(2)* is prepared by catalytic oxidation of allyl acetate *(1)* between 0 and 250 °C and



preferably under pressures of 1 to 5 bars. A redox system of palladium and copper(II) salts is claimed as the catalyst. [DOS 2220666; Farbwerke Hoechst AG, Frankfurt]

[PR 209 IE—G]

(Hydrogenated) phthalimidoacetic acid derivatives *(1)* or *(2)*, particularly derivatives *(3)* of 1-aminocyclohexanecarboxamide, are very active plant growth regulators with no harmful side effects. The compounds mainly promote growth, and



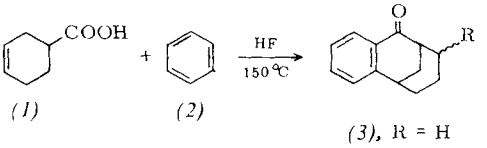
(1) *(2)* *(3)*

X = halogen, alkyl, O-alkyl, S-alkyl, N-(alkyl)$_2$, NO_2, *etc.*; n = 0–2; R^1, R^2 = alkyl (C_1–C_4) or polymethylene (C_4–C_{11}); R^3 = COOR, $CONR_2$, CN, *etc.*; X' = Cl, CH_3, CF_3

hence cause an increase in the dry weight of the plants. [DOS 2342229; American Cyanamid Co., Wayne, N. J. (USA)]

[PR 208 IE—S]

The tricyclic ketone *(3)* and its carboxylic acid *(4)* (as a *cis/trans* mixture) are obtained by reaction of 3-cyclohexenecarboxylic acid *(1)* or 1,2,3,6-tetrahydrophthalic anhydride



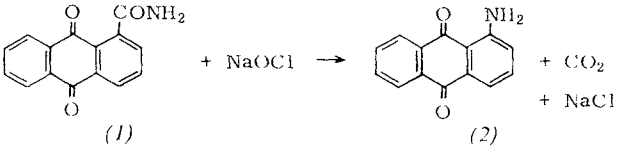
(1) *(2)*

(3), R = H
(4), R = COOH

with benzene in hydrogen fluoride. [DOS 2223127; Bayer AG, Leverkusen]

[PR 211 IE—K]

1-Aminoanthraquinone *(2)* is obtained in yields of up to 94% from anthraquinone-1-carboxamide *(1)* by a Hofmann reaction with alkali metal hypochlorite at 60—70 °C. The reaction



(1) *(2)*

can also be applied to chlorinated and brominated anthraquinones. [DOS 2222857; Badische Anilin- & Soda-Fabrik AG, Ludwigshafen]

[PR 212 IE—G]

Einführung in die metallorganische Chemie (Principles of Organometallic Chemistry). By *G. E. Coates, M. L. H. Green, P. Powell,* and *K. Wade.* Translated by *H. P. Becker, T. N. Mitchell, and W. P. Neumann.* Ferdinand Enke Verlag, Stuttgart 1972. 1st Edit., xii, 266 pp., 55 figures, 18 tables, bound DM 29.70.

"Coates" undoubtedly takes the leading place among the textbooks on organometallic chemistry. While the second edition (1960) contained the most important discoveries in this area in one volume, the third edition (1967) was produced in two volumes (together comprising some 950 pages) in spite of a sometimes very terse presentation. The normal size of a student text had surely been exceeded.

A shorter version much more suitable for teaching purposes appeared in English in 1968. Fortunately, a German translation has now been produced. It comprises a rather extensive literature survey, which takes particular account of the recently published monographs and reviews.

The contents of the book are divided into ten chapters. After an introduction in Chapter 1, three chapters deal with organometallic compounds of the main group elements and six with compounds of the transition elements. Emphasis is placed on understanding general and theoretical principles, particularly in the discussion of the transition metal compounds. For example, the reactions and structures of metal-π-complexes with monoolefins, diolefins, and polyolefins, aromatic and heterocyclic compounds, and enyl and dienyl ligands are included under one heading. For the student in the middle of his studies and for chemists not specialized in this field this is surely useful. Chapters 3 and 4 (compounds of the elements of groups 1—5) appear somewhat too detailed to the reviewer; here the limits of an introductory text have been partly exceeded.

The layout (a very sturdy binding) and printing of the German translation are unquestionably commendable. The text is very readable and is supplemented by many structural formulas, tables, and figures, usually very clearly arranged. It would be desirable for as many chemistry students as possible to use this book as a supplement to their instruction in organic and inorganic chemistry.

Helmut Werner [NB 210 IE]

Cephalosporins and Penicillins. Chemistry and Biology. Edited by *E. H. Flynn.* Academic Press, New York—London 1972. 1st Edit., xv, 752 pp., bound $ 25.—

The dominant position of penicillins and cephalosporins among the antibiotics is still unquestioned. Nearly a decade ago the chemistry in this field awoke from temporary quiescence to a surge of surprising activity. Only experts will have been able to keep abreast of the numerous studies since performed on the development of new β-lactam antibiotics; nevertheless, these investigations are frequently of interest to a broader scientific audience. The studies on the younger cephalosporin group have often served as a pacemaker, and hence it is right that the authors have from their own practical experience entitled their book starting with the cephalosporins, reversing the historical order.

The 15 chapters of this book are distinguished by their remarkable homogeneity, pleasing presentation, and easily readable English. First there is a chapter on cephalosporin C by the "father of cephalosporin chemistry" *E. P. Abraham.* Chapters follow on the preparation of 7-aminocephalosporanic acid and 6-aminopenicillanic acid, acylation and alkylation of these compounds, modifications to the dihydrothiazine ring of the cephalosporins, rearrangement of the β-lactam antibiotics, and a survey of total syntheses in this area. Subsequent chapters are concerned with structure determination by physicochemical means and analysis, and with the biology and microbiology as well as the pharmacology and toxicology of β-lactam antibiotics. An appendix contains organic preparative details and UV and NMR data. Spot checks on two rapidly developing areas (chemical deacylation of penicillins and epimerization of the β-lactam ring) underline the up-to-date presentation covering the literature up to 1970/71.

The book, edited by *Flynn*, summarizes in rational form the achievements that have taken place in the chemical and biological fields since the publication of "Chemistry of Penicillin" by *Clark, Johnson,* and *Robinson* in 1945. Like its classical predecessor, it bears the stamp of the authors' enthusiasm and pride in past successes. This topical monograph will be highly valuable to everybody working in the field of β-lactam antibiotics.

Friedrich Moll [NB 213 IE]

Nonaqueous Electrolytes Handbook, Vol. 1. By *G. J. Janz* and *R. P. T. Tomkins.* Academic Press, New York—London 1972. 1st Edit., xii, 1108 pp., bound $ 55.—.

The increasing practical importance of electrochemistry in nonaqueous solutions, *e. g.* for the electrosynthesis of organic and inorganic compounds or for titrations, makes an up-to-date index such as this very welcome. Nine sections give information on: I. The physical properties of pure nonaqueous solvents, II. purification of solvents, III. electrical conductivity of electrolyte solutions in these solvents, as well as IV. their diffusion properties, V. densities, VI. viscosities, and VII. transport numbers. Another volume with emf values, vapor pressures, cryoscopic data, heats of solution, polarographic data, and information on electrical double layers is in preparation.

Section I contains details of the melting and boiling points, dielectric constants, viscosities, densities, and specific conductivities of about 175 solvents, most of them organic, but including important inorganic solvents (among them "water-like" solvents such as DMF, DMSO, the halogens, interhalogen compounds, hydrogen halides, ammonia, *etc.*). In addition 42 binary solvent mixtures, including ones involving water, are listed. The completeness of the bibliography, at least for the last 40 years, claimed in the preface and elsewhere, has not been attained in the case of those solvents with which the reviewer is familiar; for example, the important data of *L. T. Carmichael* and *B. H. Sage* (Ind. Eng. Chem. *44*, 2728 (1952)) on the viscosity of liquid ammonia are missing.

The largest part of the book (about 750 pp.) is devoted to the tabulation of conductivity data in Section III. The solvent, the equivalent conductivity, the corresponding values of concentration and temperature, the equivalent conductivity at infinite dilution, and the literature reference are tabulated according to dissolved electrolytes, but only the solute and the reference are tabulated in the arrangement by solvents. About 650 electrolyte solutions, not only of alkali metal and ammonium salts, but also of amines, quaternary ammonium compounds, and salts of the heavy and transition metals are presented, and in certain cases solutions in mixed solvent systems are included. The authors do not aspire to the comprehensive treatment in the famous "Walden" handbook (Das Leitvermögen der Lösungen. Akademische Verlagsgesellschaft, Leipzig 1924).

It is not clear why there is a Section VIII A, because although the data on DMSO and anhydrous sulfuric acid have already been treated in Sections I—VII they appear here again, though in somewhat greater detail. These details, as well as further literature on the purification of solvents, electrical conductivity, diffusion, density, viscosity, and transport numbers, which are relatively new, are intended as a recent supplement to Sections I—VII. It would be preferable if Section VIII B, in which general references to the larger reference works are given, also contained references to the appropriate German books (*e.g.* Chemie in nichtwäßrigen ionisierenden Lösungsmitteln. Vieweg, Braunschweig 1960, in which electrochemistry is emphasized).

Finally, Section IX contains lists of solvents and solutes, making this very welcome book a more than useful addition to the bookshelf.

Jochen Jander [NB 214 IE]

Lehrbuch der Pharmakognosie. Auf phytochemischer Grundlage. [Textbook of Pharmacognostics. The Phytochemical Basis]. By *E. Steinegger* and *R. Hänsel*. 3rd Edit., Springer Verlag. Berlin—Heidelberg—New York 1972. xii, 557 pp., 5 illustrations, bound DM 78.—.

This is the third edition of a textbook on theoretical pharmacognostics, *i.e.* it contains almost nothing of the traditional approach to practical recognition of drugs, no microscopic morphology, no sections, no plant hairs, *etc.* There are only occasional references to botany and to the distinguishing characteristics of drugs, and what is probably meant by the term "pharmaceutical biology" in the new examination statutes for pharmacists in the German Federal Republic appears to have been neglected. For example, the term "assimilation" does not occur, and in the description of the nucleic acids and ATP the importance of these compounds in the context of genetic information and energy metabolism is not discussed.

By being restricted purely to the phytochemical description of natural products, the 557 pages of text offer, on the other hand, an impressive amount of descriptive matter. The work is a virtual mine of information on natural products, especially on the secondary plant products. The latest results of research are recognized, selected according to pharmaceutical importance, and as far as possible with data on the pharmacology and, when appropriate, on isolation and processing.

A modest plea is made for the inclusion of plant-derived drugs with subtle and, in certain cases undetectable, effects in model tests (these are special areas which are of considerable importance in Europe). Biosynthetic pathways are often given, but, commendably, not taken as proven. The occasional remarks on etymology and history provide pleasant relaxation for the reader. (But *Leonhard Fuchs* is introduced incorrectly as a medical doctor from Frankfurt; he was in fact a professor at Ingolstadt and later at Tübingen.) References to the original literature facilitate the identification of sources. All in all, this is an interesting, valuable, and practical book, well worth the money, and giving complete information on what is of interest to the chemically-oriented pharmacist or physician.

Engelbert Graf [NB 216 IE]

The Biochemistry of the Nucleic Acids. By *J. N. Davidson*. Science Paperbacks. Chapman & Hall, London 1972. 7th Edit., xiv, 396 pp., numerous figures, bound £ 2.25.

Anybody who has long been concerned with nucleic acids will still remember the small book, from which he obtained his first thorough and profound knowledge of this area 20 years ago, and which has remained a constant companion with some updating revisions. In all its editions "Davidson" has been a reliable guide to the increasingly complex field which in other respects was becoming clearer. While formerly the analytical composition and the physical chemistry of the polar sugar phosphate skeleton, the base-pairing laws, and finally the helical molecular structure were the undisputed backbone of the field, now it is the biological functions during the transformation of the genetic code into proteins and enzymes that are in the foreground. The predominant part of the book is therefore devoted to the molecular conformations of ribonucleic and deoxyribonucleic acids, the biosynthetic processes taking place in the replication and transcription, as well as the anabolism and catabolism of nucleic acid components.

From decades of experience the author has mastered the subject, and the most recent literature has been carefully chosen, with a wide selection in each chapter. Clear and informative diagrams in addition to impressive illustrations further assist understanding. The presentation is often simplified, but always balanced and critical. There are no obvious mistakes but, as can be expected, information has accrued or become out of date. The text is clear and lucidly written and does not present difficulties even for beginners, so that this guide can be considered to be the best comprehensive introduction for biologists and chemists to the biochemistry of the nucleic acids and should be read by as many as possible.

L. Jaenicke [NB 218 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal.

Struktur und Bindung – Atome und Moleküle. By *G. Grossmann, J. Fabian*, and *H.-W. Kammer*. Lehrbuch 1 of "Fachstudium Chemie". Verlag Chemie, Weinheim 1973, 232 pp., stitched, DM 25.00.

Struktur und Bindung – Aggregierte Systeme und Stoffsystematik. By *J. Sieler, E. Butter, G. Haucke, G. Kühn, and A. Martin*. Lehrbuch 2 of "Fachstudium Chemie". Verlag Chemie, Weinheim 1973. 212 pp., stitched, DM 25.00.

Controlled Action Drug Forms. By *J. C. Colbert*. Vol. 24 of the series "Chemical Technology Reviews". Noyes Data Corporation, Park Ridge 1974. XII, 337 pp., bound, $ 36.00.

An Introduction to Conservation of Orbital Symmetry. A Programmed Text. By *A. J. Bellamy*. Longman Group Ltd., London 1974. X, 77 pp., stitched, £ 1.50.

Foams. By *J. J. Bikerman*. Vol. 10 of the Series "Applied Physics and Engineering". Springer-Verlag, Berlin 1973. IX, 337 pp., bound, DM 61.60.

Acid Sulphate Soils. 18. Publication of the International Institute for Land Reclamation and Improvement, Wageningen 1973. Vol. I: Introductory Papers and Bibliography, Vol. II: Research Papers. Edited by *H. Dost*. Vol. I: XIV, 295 pp.; Vol. II: 406 pp.—Proceedings of the International Symposium, 13—20 August 1972, Wageningen.

Chemische Carcinogene im Laboratorium. Struktur, Wirkungsweise und Maßnahmen beim Umgang. By *U. Wölcke*. Vol. 3 der Schriftenreihe Arbeitsschutz. Bundesanstalt für Arbeitsschutz und Unfallforschung, Dortmund 1974. 47 pp., stitched, DM 9.80.

Ascorbinometric Titrations. By *L. Erdey* and *G. Svehla*. Akadémiai Kiadó, Budapest 1973. 183 pp., bound, DM 21.20.

Prüfungsfragen Chemie für Mediziner. 100 Multiple-Choice-Fragen mit einer Anleitung zur Bearbeitung. By *K. Beyermann, Ch. Braig, J. Sauer*, and *A. Zeeck*. Vol. 17 of the Series "Taschentext". Verlag Chemie/Physik Verlag Weinheim 1974, 99 pp., stitched, DM 8.80.

Reaktionsverhalten und Syntheseprinzipien. By *E. Uhlig, G. Domschke, S. Engels, B. Heyn*, and *D. Walter*. Lehrbuch 7 of "Fachstudium Chemie". Verlag Chemie, Weinheim 1973. 408 pp., stitched, DM 39.80.

Theory of Unimolecular Reactions. By *W. Forst*. Vol. 30 of the Series "Physical Chemistry". Edited by *E. M. Loebl*. Academic Press New York 1973. XV, 445 pp., bound. $ 29.50.

Polymer Spectroscopy. Edited by *D. O. Hummel*. Vol. 6 of the Series "Monographs in Modern Chemistry". Edited by *H. F. Ebel*. Verlag Chemie, Weinheim 1974. XII, 401 pp., bound, DM 125.—.

Mathematics for Engineers and Scientists. By *A. Jeffrey*. From the Series "Applications of Mathematics". Edited by *A. Jeffrey*. Thomas Nelson & Sons Ltd., London 1971. X, 765 pp., stitched, £ 3.00.

Free-Radical Chemistry. By *D. C. Nonhebel* and *J. C. Walton*. Cambridge University Press, London 1974. XV, 572 pp., bound, £ 15.00.

Organische Stereochemie. Begriffe und Definitionen. By *W. Bähr* and *H. Theobald*. Vol. 131 of "Heidelberger Taschenbücher". Springer-Verlag, Berlin 1973. xv, 122 pp., stitched DM 16.80.

Zeolite Molecular Sieves. Structure, Chemistry, and Use. By *D. W. Breck*. John Wiley & Sons, New York 1974. ix, 771 pp., bound £ 18.00.

Anorganische Chemie. By *F. A. Cotton* and *G. Wilkinson*. Verlag Chemie/Interscience Publishers 1974. 3rd completely revised edition, xv, 1235 pp., bound DM 88.00.

Chemisches Rechnen auf elementarer Grundlage in Form einer Aufgabensammlung. By *H. Fiedler*. Verlag Chemie, Weinheim 1973. 2nd impression of the 7th revised edition, 367 pp., stitched DM 22.00.

Grundzüge der Astronomie. By *B. Müller*. Vol. 12 of the series "Taschentext". Verlag Chemie/Physik Verlag, Weinheim 1973. 189 pp., stitched DM 16.80.

Strukturaufklärung—Spektroskopie und Röntgenbeugung. By *K. Doerffel, D. Beyer, J. Brunn, W. Höbold, D. Kirsch*, and *G. Lux*. Lehrbuch 3 des "Fachstudiums Chemie". Verlag Chemie, Weinheim 1973. 144 pp., stitched DM 18.80.

Strukturaufklärung—Spektroskopie und Röntgenbeugung. By *E. Steger, B. Adler, J. Brunn, K. Doerffel, W. Höbold, J. Krause, A. Mehlhorn, E. Müller*, and *D. Treibmann*, Arbeitsbuch 3 des "Fachstudiums Chemie". Verlag Chemie, Weinheim 1973. 296 pp., stitched DM 29.80

Chemische Kinetik. By *K. Schwetlick, H. Dunken, G. Pretzschner, K. Scherzer*, and *H.-J. Tiller*. Lehrbuch 6 des "Fachstudiums Chemie". Verlag Chemie, Weinheim 1973. 186 pp., stitched DM 22.00.

Chemotaxis and Inflammation. By *P. C. Wilkinson*. Churchill Livingstone, Edinburgh 1974. 214 pp., bound £ 4.00

Enzyme. Gewinnung—Analyse—Regulation. By *A. Betz*. Verlag Chemie, Weinheim 1974. ix, 197 pp., Paperback DM 28.80.

The Chemistry of the Non-Metals. By *P. Powell* and *P. Timms*. Chemistry Textbook Series. Chapman and Hall, London 1974. xii, 281 pp., stitched £ 2.85.

Contents: Principles of Structure and Bonding; Simple Hydrides and Halides; Non-Metal Oxides, Sulphides, and Their Derivatives; The Elements; Catenated Compounds and Related Systems: Borazines, Phosphazenes, Silicones, and Related Systems.

Principles and Applications of Electrochemistry. By *D. R. Crow*. Chemistry Textbook Series. Chapman and Hall, London 1974. v, 228 pp., stitched £ 2.40.

Inorganic Solids. An Introduction to Concepts in Solid-State Structural Chemistry. By *D. M. Adams*. John Wiley & Sons, London 1974. xvi, 335 pp., bound £ 7.50, stitched £ 3.50.

Contents: Preliminaries; Some Basic Concepts; What Structures are Possible? Predictions on the Basis of Close-Packing; Predictions on the Basis of Bond Type; Furthers Factors Affecting Crystal Structure; Molecular and Hydrogen-Bonded Crystals; More about Mainly Covalent Crystals; The Metallic Elements; Degrees of Order.

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Volume 13 · Number 10
October 1974
Pages 619–682

The Synthesis of Unusual Organic Molecules Using Cyclic Peroxides

New synthetic methods (3)

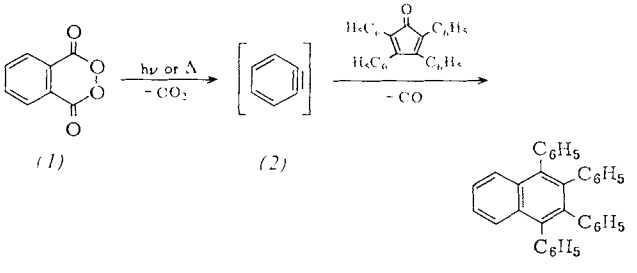
By Waldemar Adam[*]

The photodecarboxylation of malonyl peroxides into α-lactones[1] and the thermal conversion of the 1,4-*endo*-peroxide 4,5-epoxy-3,6-epidioxy-1-cyclohexene into the novel benzene trioxide[2] are two recent examples of the potential of cyclic peroxides in the synthesis of unusual organic molecules. The former transformation entails a fragmentation, the latter a rearrangement process. Most reported examples fall into one of these two gross reaction types. Of the numerous examples that have been reported in the literature during the last two decades, only those shall be focused on that lead to unusual compounds or constitute efficient syntheses of known compounds, in order to stress the convenience of cyclic peroxides in the synthesis of organic compounds.

1. Fragmentation Reactions

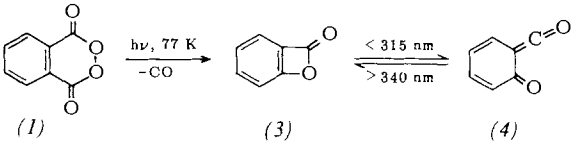
1.1. Decarboxylations

An early example of the utility of decarboxylative fragmentations of cyclic peroxides was recognized by *Greene*[3] in the attempt to prepare dehydrobenzene *(2)* from phthaloyl peroxide *(1)*. Although thermolysis of *(1)* in solution was complicated due to free radical induced decompositions, on thermolysis in the gas phase *Wittig* and *Ebel*[4] were able to trap the dehydrobenzene *(2)* with tetraphenylcyclopentadienone. Similar observations were made by *Horner* and *Brüggemann*[5] and by *Jones* and *DeCamp*[6].



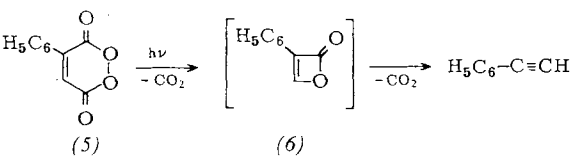
(1) *(2)*

In contrast, photodecarboxylation of *(1)* at 77 K afforded the oxoketene *(4)* employing matrix isolation techniques[7]. In this work the lactone *(3)* was postulated as precursor



(1) *(3)* *(4)*

of *(4)*. Indeed, *Chapman et al.*[8] confirmed the presence of the unsaturated β-lactone *(3)* on irradiation of *(1)* in an Argon matrix at 8 K with long wavelength (>340 nm) light. At shorter wavelengths (<315 nm) the lactone *(3)* could be quantitatively converted into its valence tautomer *(4)*, while *(3)* could be regenerated from *(4)* at the longer wavelength. Similarly the lactone *(6)* was proposed as intermediate in



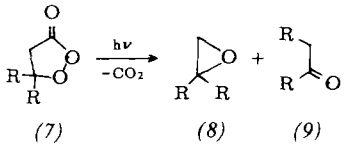
(5) *(6)*

the thermo- and photodecarboxylation of the phenylmaleoyl peroxide *(5)*[9].

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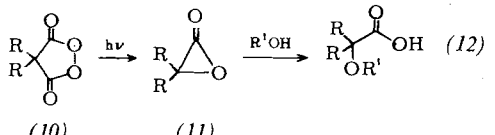
[**] A. P. Sloan Fellow 1968–72; J. S. Guggenheim Fellow 1972–1973.

1,2-Dioxolan-3-ones (β-peroxylactones) *(7)* photodecarboxylate[10] into epoxides *(8)*; in addition, minor amounts of ketones *(9)* are formed by rearrangement. In the thermal decarboxylation[11] of compound *(7)* ketones are formed exclusively.



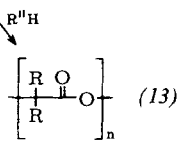
(7) *(8)* *(9)*

Hence, it appeared sensible to photodecarboxylate malonyl peroxides *(10)* in the hope of obtaining the rather difficultly accessible α-lactones *(11)*[12]. Indeed, irradiation[13] of alcoholic solutions of di-*n*-butylmalonyl peroxide *(10a)* afforded high yields (>90%) of the α-alkoxy acid *(12a)*, which was presumably formed by trapping of *(11a)* with alcohol. In



(10) *(11)* *(12)*

(a), R = n-C_4H_9
(b), R = CH_3
(c), R-R = -$(CH_2)_2$-
(d), R-R = -$(CH_2)_3$-
(e), R-R = -$(CH_2)_4$-

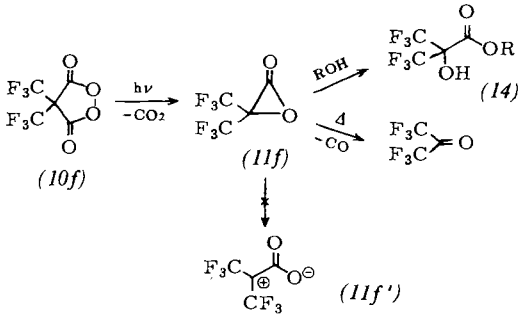


(13)

hydrocarbon solvents R″H the polyester *(13)* was obtained quantitatively.

The formation of α-lactones could be confirmed[1b] by irradiation of malonyl peroxides *(10)* in a matrix at 77 K, whereby the characteristic carbonyl band appeared at 1895 cm^{-1}. On prolonged photolysis, the α-lactones suffered decarbonylation, while on warming to 180 K polymers of type *(13)* were formed.

The preparation of an authentic α-lactone, which is stable at room temperature (half-life *ca.* 8 h in the gas phase), has been accomplished recently[1c]. Electronic destabilization of the dipolar valence tautomer *(11f′)* utilizing trifluoromethyl substituents, favored the formation of the cyclic valence tau-

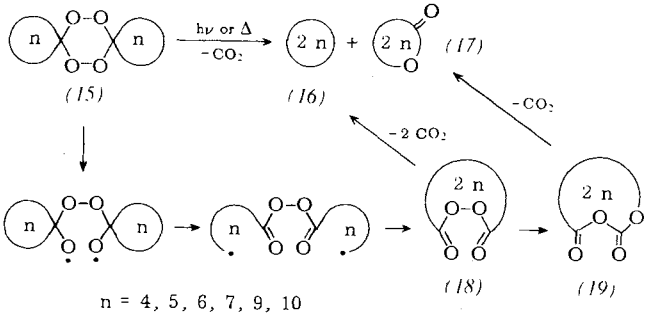


(10f) *(11f)* *(14)* *(11f′)*

tomer *(11f)* in the photolysis of the malonyl peroxide *(10f)*. While α-lactone *(11f)* is stable in nonpolar solvents for weeks at −20 °C, on heating it decarbonylates to give perfluoroacetone. Alcoholysis leads to the α-hydroxy ester *(14)* instead of the usual α-alkoxy acid *(12)*[1a], thus demonstrating very dramatically the "cyclic" chemical behavior of this lactone.

Since malonyl peroxides *(10)* are readily available in high yields from the corresponding malonic acids[13], photodecarboxylation provides the most expedient synthesis so far of the interesting α-lactones *(11)*.

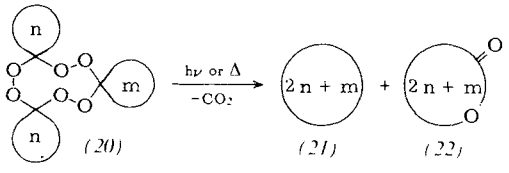
An ingenious decarboxylative fragmentation has been reported by *Story et al.*[14]; it consists in the thermolysis and photolysis of dimeric peroxides of type *(15)*, leading to the carbocycles



(15) *(16)* *(17)* *(18)* *(19)*

n = 4, 5, 6, 7, 9, 10

(16) and lactones *(17)*. Here the spirocarbons serve as potential carbon dioxide leaving groups. For example, rupture of the peroxide bond, double β-scission, and finally coupling presumably affords the cyclic diacyl peroxide *(18)*. The latter decarboxylates directly into the carbocycle *(16)* or suffers carboxy inversion[15] to give *(19)*, which subsequently decarboxylates into the lactone *(17)*. Although this mechanism still lacks chemical verification, it is consistent with CIDNP (chemically induced dynamic nuclear polarization) data[16].



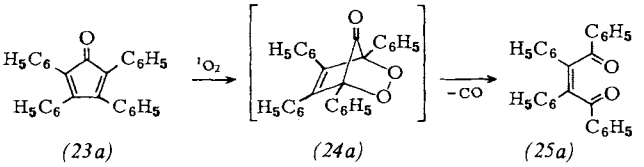
(20) *(21)* *(22)*

n = 5, 6, 7, 11, 12; m = 5, 6, 7, 9, 11, 12,

The trimeric peroxides *(20)* decarboxylate in a similar way to give carbocycles *(21)* and lactones *(22)*. In view of the ready availability of dimeric and trimeric peroxides, the impressive feature of these decarboxylations is that they provide a simple route to the synthesis of macrocyclic hydrocarbons and esters that are otherwise quite difficult to prepare.

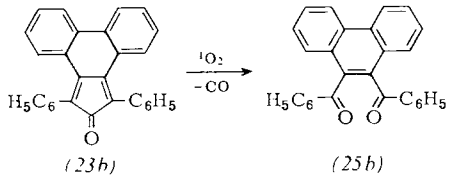
1.2. Decarbonylations

Interesting examples of decarbonylative fragmentation of cyclic peroxides are scarce, but a potentially useful *cis*-diacylation method worthwhile mentioning is the oxidation of cyclopentadienones with singlet oxygen. Thus, addition of photochemically[17] and chemically[18] generated singlet oxygen to tetraphenylcyclopentadienone *(23a)* affords moderate yields (35 to 65%) of *cis*-dibenzoylstilbene *(25a)*, presumably by fragmentation of the intermediary peroxide *(24a)*. Two well known

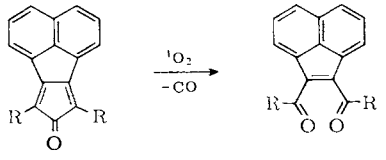


(23a) *(24a)* *(25a)*

examples are the preparation of 9,10-dibenzoylphenanthrene *(25b)* from *(23b)*[19] and of 1,2-diacylacenaphthylene derivatives *(25c)* and *(25d)* from *(23c)* and *(23d)*[20].



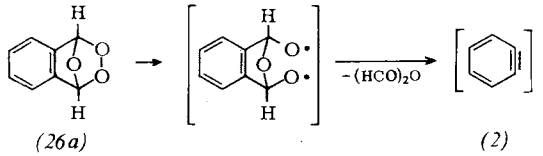
(23b) *(25b)*



(23c) R = isopropyl *(25c)*
(23d) R-R = $-(CH_2)_{12}-$ *(25d)*

1.3. Fragmentation of Ozonides

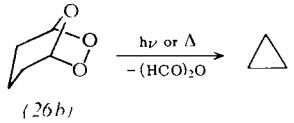
In contrast to 1,2-dioxolanes, such as *(7)* and *(10)*, which are thermally and photochemically converted into epox-



(26a) *(2)*

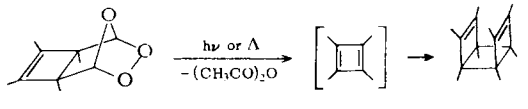
ides [21], the related 1,2,4-trioxolanes or ozonides *(26)* suffer double β-scission, resulting, in the case of the ozonide *(26a)*, in the formation of dehydrobenzene *(2)*[22]. However, it required almost a decade for this interesting fragmentation to be exploited for synthetic purposes[23].

Photochemically, as well as thermally, the ozonide *(26b)* affords a 35—40% yield of cyclopropane as major product.



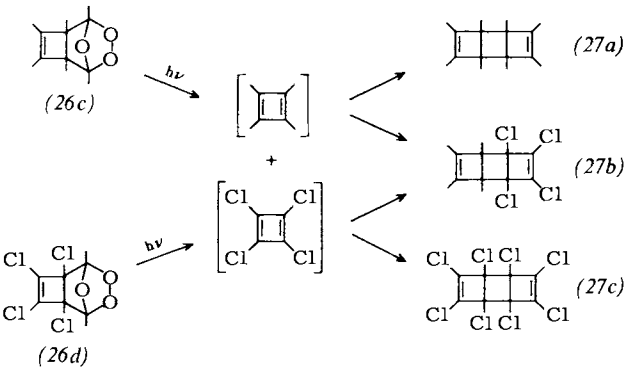
(26b)

Similarly, photolysis of the ozonide *(26c)* derived from hexamethyl(Dewar benzene) gave the *syn*-dimer *(27a)* of tetramethylcyclobutadiene[24].



(26c) *(27a)*

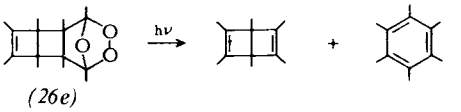
Independently of this work, *Criegee et al.*[25] greatly extended the scope of this novel reaction. They found that the ozonide *(26d)* afforded the *syn*-dimer *(27c)*. This reaction probably proceeds *via* the cyclobutadiene derivative, since the *syn*-dimer *(27b)* is also formed on photolysis of a mixture of ozonides *(26c)* and *(26d)*. This useful olefin synthesis proved to be a highly stereospecific (*ca.* 90%) *cis* reaction, as could be



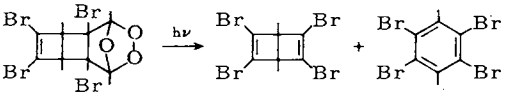
(26c) *(27a)* *(27b)* *(27c)* *(26d)*

demonstrated on using the ozonides derived from *cis*- and *trans*-1,2,3,4-tetramethylcyclobutene[25a].

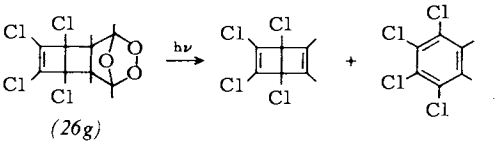
A rather clever utilization of this reaction was the synthesis of hexamethyl(Dewar benzene) from ozonide *(26e)*. The



(26e)

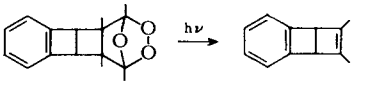


(26f)



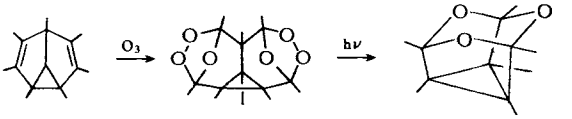
(26g)

ozonides *(26f)* and *(26g)* react analogously. The photolysis of ozonide *(26h)* led, in a similar way, to a Dewar naphthalene derivative[26].



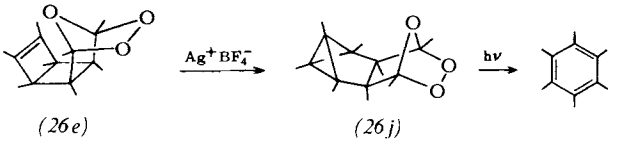
(26h)

A rather ingenious attempt at preparing tetramethyltetrahedrane utilized the photolysis of the diozonide *(26i)* derived from octamethylsemibullvalene[25a]; in addition to a host of other products, the novel triketal *(28)* was also formed. An



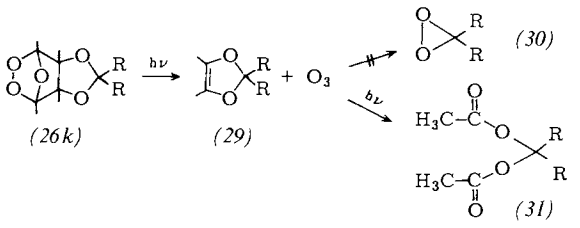
(26i) *(28)*

inventive route to hexamethylbenzvalene *via* photolysis of the ozonide *(26j)* failed, disappointingly yielding only hexamethylbenzene[27].



(26e) *(26j)*

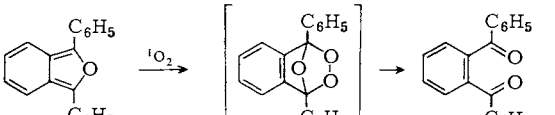
It could also be demonstrated that the photolysis of ozonide *(26k)* constitutes a convenient route to the synthesis (40 to 60% yields) of 1,3-dioxolenes *(29)*[25c]. However, an attempt



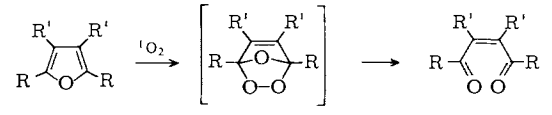
(26k) *(29)* *(30)* *(31)*

to prepare the so far unknown 1,2-dioxirane *(30)* by ozonolysis of *(29)* gave the novel acetal *(31)*[25c].

On the other hand, unsaturated ozonides prepared by oxidation of furans with singlet oxygen suffer a completely different fragmentation. A well known example is the oxidation of 2,5-diphenyl-3,4-benzofuran[28] to 1,2-dibenzoylbenzene, which probably proceeds *via* the intermediary ozonide *(261)*; however, the course of the reaction has not as yet been elucidated. This reaction, which is similar to the decarbonylation discussed in Section 1.2, could be utilized for *cis*-diacylations[29], as shown in the cases *(26m)*—*(26p)*. A fascinating example of this reaction was observed by *Wasserman* and



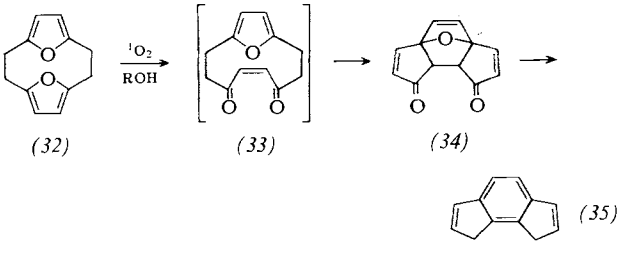
(261)



(26m)-*(26p)*

(m), R = R' = H[29b] *(o)*, R = R' = C_6H_5[29a]
(n), R = CH_3, R' = H[29c] *(p)*, R = C_6H_5, R' = H[29a]

Doumaux[30] in the $^1O_2$ oxidation of the furanophane *(32)*, leading to the epoxydiketone *(34)* *via* intramolecular Diels-Alder addition of the intermediary enedione *(33)*. *Katz*

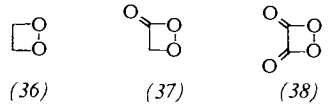


(32) *(33)* *(34)* *(35)*

et al.[31] employed this unusual transformation to obtain dihydro-*as*-indacene *(35)*, the precursor required to prepare *bis*(*as*-indacenyliron).

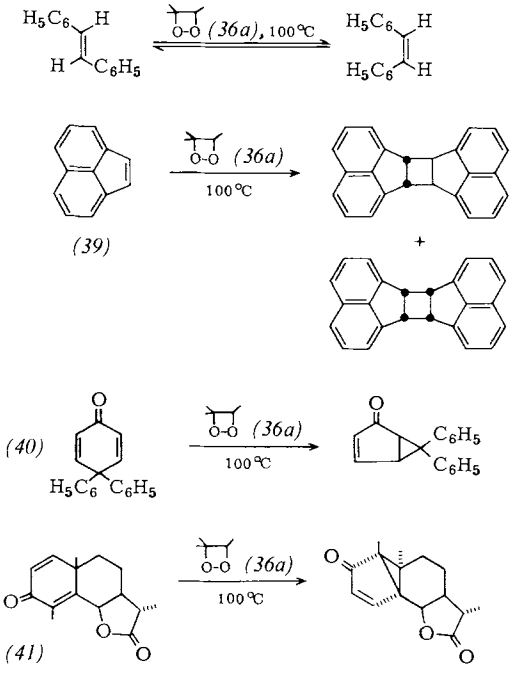
1.4. Chemielectronic Fragmentations

The discovery that four-membered cyclic peroxides such as the 1,2-dioxetanes *(36)*[32], the 1,2-dioxetanones (α-peroxylactones) *(37)*[33], and the carbon dioxide dimer *(38)*[34] lead to triplet energized carbonyl products on fragmentation, opens



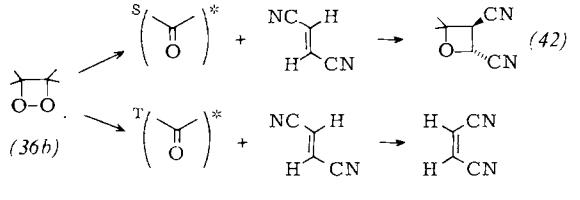
(36) *(37)* *(38)*

up exciting possibilities of performing photoreactions "thermally". By using trimethyl-1,2-dioxetane *(36a)* as energizer it was possible to promote the *cis-trans* isomerization of stilbene, the dimerization of acenaphthene *(39)*, the isomerization of 4,4-diphenyl-2,5-cyclohexadienone *(40)*, and the conversion of santonin *(41)* into lumisantonin *(42)*[35]. Similarly, the di-



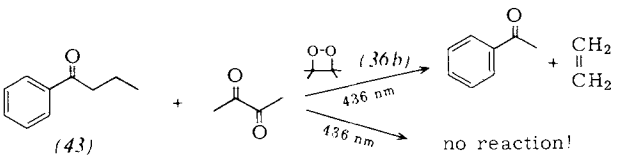
(39) *(40)* *(41)*

merization of pyrimidines in *E. coli* DNA could be chemically energized by 1,2-dioxetanes[36]. *Turro* and *Lechtken*[37] have demonstrated that 1,2-dioxetane *(36b)* fragments into singlet excited acetone, which adds to *cis*-1,2-dicyanoethylene to give oxetane *(42)* and triplet excited acetone which effects *cis-trans* isomerization of the dicyanoethylene. A further important experiment is the biacetyl sensitized fragmentation of *n*-butyro-



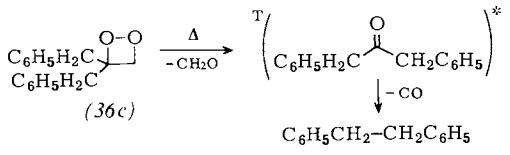
(36b) *(42)*

phenone *(43)*, which succeeds only in the presence of 1,2-dioxetane *(36b)*[38]. In another example triplet-excited dibenzyl phenone *(43)*, produced by fragmentation of 1,2-dioxetane *(36c)*, suffered decarbonylation[39]. Finally, by using the car-



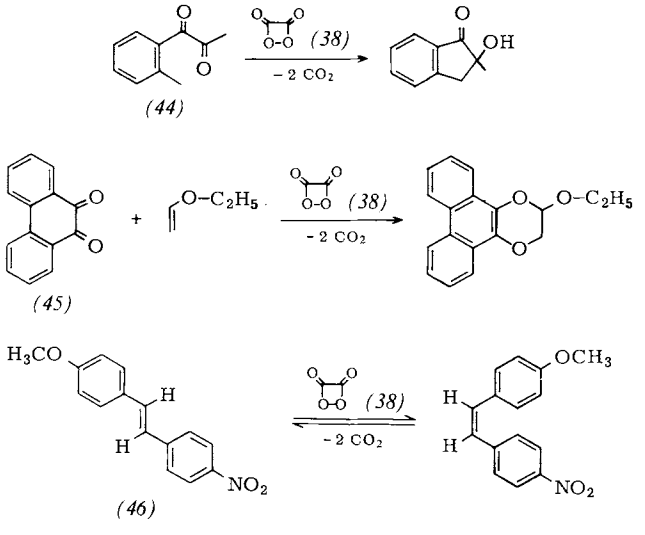
(43)

bon dioxide dimer (38) as energizer, α-diketone (44) could be cyclized[40], ethoxyethylene cycloadded to 9,10-phenanthra-



(36c)

quinone (45), and *p*-methoxy-*p'*-nitrostilbene (46) *cis-trans* isomerized.



(44)

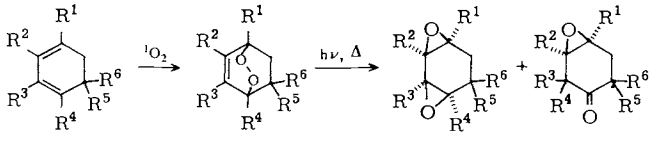
(45)

(46)

2. Rearrangements

2.1. Epidioxides

It has long been known that some epidioxysteroids are thermally and photochemically labile[41], but this knowledge was first exploited for syntheses in 1945 by *Schenck* and *Ziegler*[42]. These authors showed that the diversely substituted peroxides (48), which are readily accessible by oxidation of the 1,3-dienes (47) by singlet oxygen, generally form the diepoxides (49)



(47) (48) (49) (50)

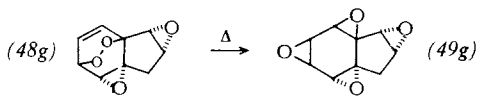
(a), $R^1 = CH_3$, $R^2 = R^3 = R^5 = R^6 = H$, R^4 = Isopropyl
(b), $R^1 - R^6 = H$
(c), $R^1 = R^3 = R^5 = R^6 = CH_3$, $R^2 = R^4 = H$
(d), $R^1 = R^4 = C_6H_5$, $R^2 = R^3 = R^5 = R^6 = H$
(e), $R^1 - R^5 = C_6H_5$, $R^6 = H$
(f), $R^1 = R^3 = R^4 = R^5 = H$, $R^2 = CH_3$, R^6 = Isopropyl

and epoxyketones (50). The latter presumably result from further rearrangement of the diepoxide (49) (cf. Ref. [43]).



(51) (52)

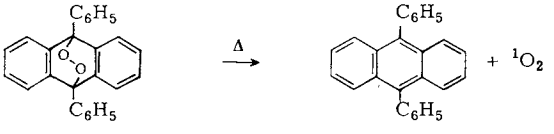
The synthesis of benzene trioxide (52) by thermal rearrangement of epoxyperoxide (51) has already been mentioned[2]. A further example is the thermal conversion of the endoperoxide (48g) into the tetraepoxide (49g)[44]. The prep-



(48g) (49g)

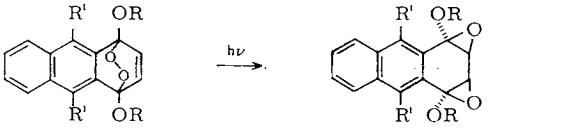
aration of such unusual molecules by conventional synthetic techniques would certainly be cumbersome.

Singlet oxygen is liberated almost quantitatively on refluxing the peroxide (53a) of 9,10-diphenylanthracene (54a) in benzene; this reaction constitutes an excellent chemical source



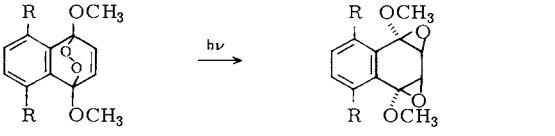
(53a) (54a)

of $^1O_2$[45]. In contrast, peroxides with bridgehead alkoxy groups, such as the anthracene derivatives (53b)—(53e) and the naphthalene derivatives (53f) and (53g), undergo the diepoxide rearrangement[46] mentioned already for the alipha-



(53b)–(53e) (54b)–(54e)

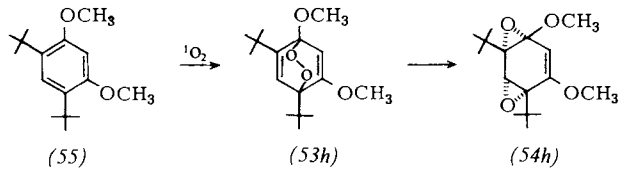
(b), R = CH_3, R' = H
(c), R = C_2H_5, R' = H
(d), R = $CH_2C_6H_5$, R' = H
(e), R' = CH_3, R' = C_6H_5



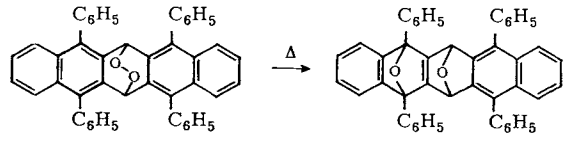
(53f), (53g) (54f), (54g)

(f), R = H
(g), R = C_6H_5

tic systems. Even the resorcinol derivative (55) is sufficiently activated to add singlet oxygen; this affords the peroxide (53h), which also undergoes the diepoxide rearrangement[47], and thus constitutes one of the few examples from the benzene series[48]. The mechanism of the unusual rearrangement of the peroxide (53i) into the diepoxide (56) is still unclear[49].

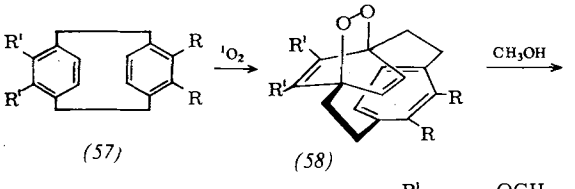


(55) (53h) (54h)



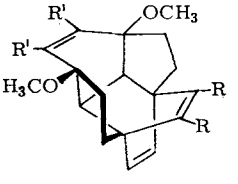
(53i) (56)

Even more unusual are the paracyclophanes *(57)*. On oxidation with singlet oxygen the intermediary peroxides *(58)* that are formed undergo intramolecular Diels-Alder addition with concomitant methanolysis, resulting in polycyclic molecules *(59)*[50].



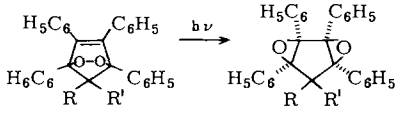
(57) (58)

(a), R = H, R' – R' = Benzo
(b), R – R = R' – R' = Benzo



(59)

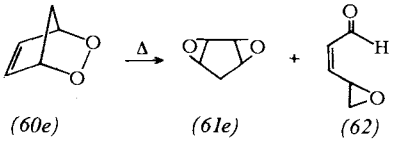
Peroxides *(60)* derived from 1,3-cyclopentadienes are considerably more thermally labile than those from 1,3-cyclohexadienes *(48)* and give rather impure products; but photochemically they undergo the diepoxide rearrangement cleanly and



(60) (61)

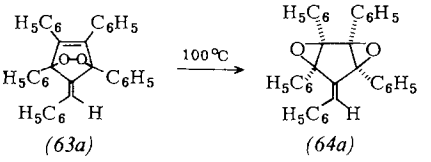
(a), R = R' = H *(c)*, R = H, R' = C_6H_5
(b), R = H, R' = C_2H_5 *(d)*, R = CH_3, R' = C_6H_5

afford *(61)* in good yields (60—95 %)[51]. Thermolysis of the unsubstituted system *(60e)* yields the epoxyaldehyde *(62)* as major product, along with some of the expected diepoxide *(61e)*[52].



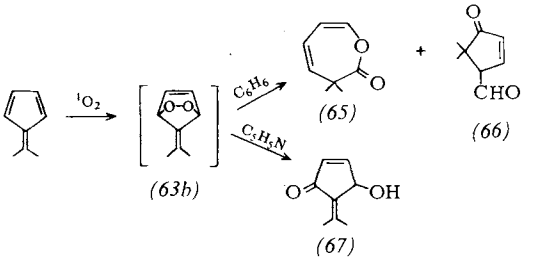
(60e) (61e) (62)

In the thermal rearrangement of epidioxyfulvenes *(63)*[53] in xylene the diepoxide *(64a)* is formed as major product from the pentaphenyl derivative *(63a)*.



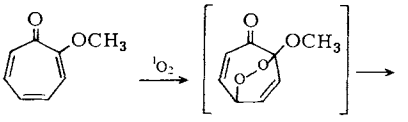
(63a) (64a)

Considerable deoxygenation to the fulvene also occurs. However, photooxidation of dimethyl fulvene[54] in benzene leads to mixtures of the oxepinone *(65)* and the oxocyclopentenecarbaldehyde *(66)* in very good yield. In pyridine as solvent, the hydroxycyclopentenone *(67)* is formed. Both reaction paths were postulated to involve the intermediary epidioxyfulvene *(63b)*. *Uda et al.*[55] have recently shown that the photooxidation of fulvenes provides a convenient route to the oxepinones *(65)* in moderate yields (20—26 %). These compounds are otherwise difficult to prepare.

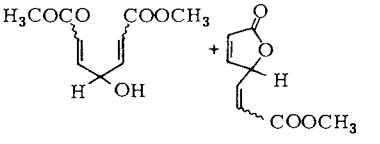


(63b) (65) (66) (67)

In the case of tropones, it has been observed that thermal rearrangement[56] leads to complex mixtures, which derive

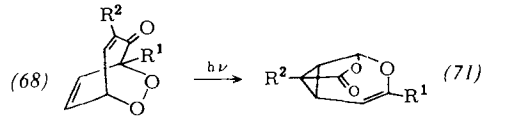


(68a)



(69) (70)

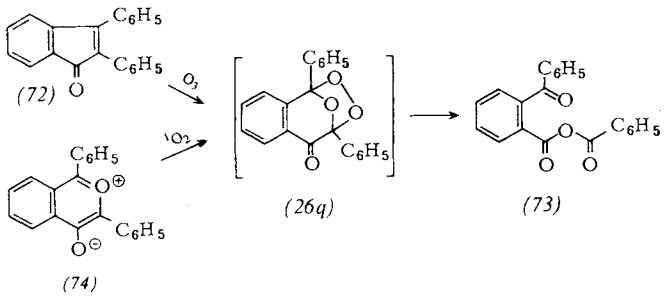
from the labile diester *(69)* and labile lactone ester *(70)*. On the other hand, photolysis of *(68)* yields the bicyclic lactones *(71)*—an interesting synthesis of these novel compounds[57].



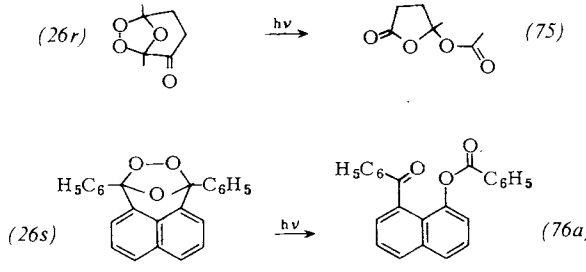
(68) (71)

2.2. Ozonides

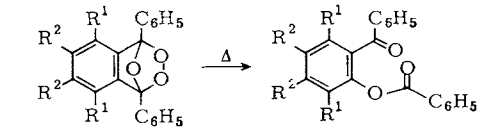
Interesting ozonide rearrangements of synthetic potential are much less numerous. However, *Criegee et al.*[58] have already observed that the ozonide *(26q)*, which is formed in the ozonolysis of indenone *(72)*, undergoes thermal rearrangement into the oxoanhydride *(73)*. The same ozonide *(26q)* could also be prepared by addition of singlet oxygen to the zwitter ion *(74)*[59]. Similarly, an attempt to prepare cyclopro-



panone from ozonide *(26r)* by photoextrusion of acetic anhydride resulted in the rearrangement product *(75)*[25c]. *Story*

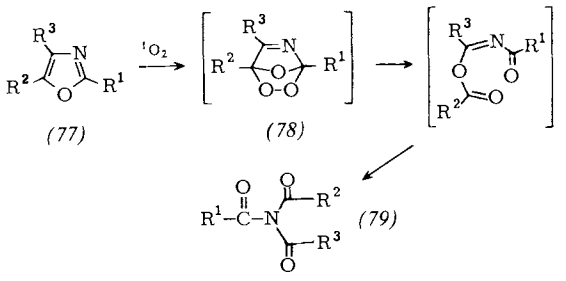


et al.[24] also observed this type of rearrangement in the photolysis of ozonide *(26s)*, a potential source of the diradical 1,8-naphthalenediyl. The oxoester *(76a)* was the major reaction product. Quite related is the recent finding that derivatives of ozonide *(26l)* rearrange into oxoesters *(76b)*[60].



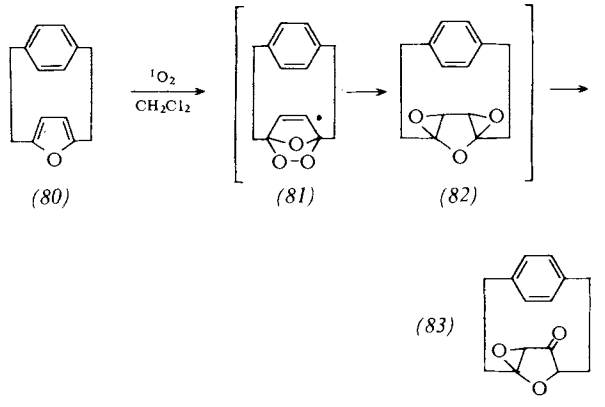
$R^1 = R^2 = H$; $R^1 = C_6H_5$, $R^2 = H$; $R^1 = R^2 = C_6H_5$

The addition of singlet oxygen to oxazoles *(77)*, which leads *via* thermal rearrangement of the intermediary ozonides *(78)*

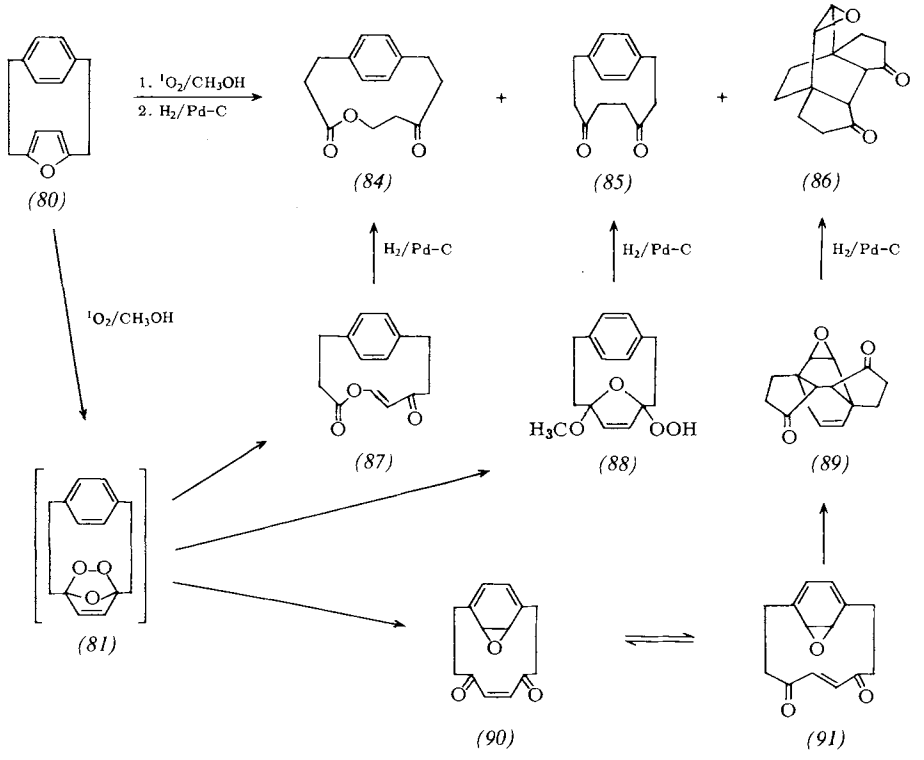


to the novel triacylamines *(79)* in high yield, should be of unquestionable synthetic value. The mechanism has been established by ^{18}O-labeling experiments[61]

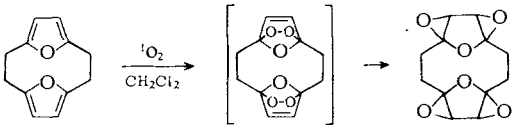
Finally, two interesting rearrangements of ozonides have been observed in the $^1O_2$-oxidation of phanes. For example, the phane *(80)* reacts in dichloromethane to give the epoxyketone



(83), which is thought to arise by rearrangement of the ozonide *(81)* to the diepoxide *(82)*[62].



Still more bewildering is the oxidation of *(80)* in methanol. The catalytic hydrogenation of the photooxidized products led to *(84)*, *(85)*, and *(86)*[62]. The formation of the oxoester *(84)* from ozonide *(81)* is readily understood if one assumes that *(81)* rearranges analogously to *(26s)*; initially, *(87)* is formed. The diketone *(85)* is formed, *via* the hydroperoxide *(88)*, by methanolysis of ozonide *(81)*. However, some rather unusual transformations of ozonide *(81)* must take place to produce the observed polycyclic epoxydiketone *(86)*. For example, transannular epoxidation of the benzene ring in *(81)* gives *(90)*, which *cis-trans* isomerizes into *(91)* and, after subsequent intramolecular Diels-Alder addition, finally affords the compound *(89)*. The second example is the conversion of furanophane *(32)*, *via* the diozonide *(92)*, into the tetraepoxide *(93)*[63].



(32) *(92)* *(93)*

3. Conclusion

The examples collected in this article concerning fragmentations and rearrangements of cyclic peroxides reveal quite effectively the synthetic potential of these compounds. Particularly valuable are the decarboxylations of cyclic diacyl peroxides for the synthesis of strained small rings. On the other hand, the synthesis of macrocycles by the Story fragmentation of spiro ketone peroxides is truly impressive. Also the stereospecific introduction of double bonds *via* the photolytic fragmentation of ozonides will prove to be of unquestionable synthetic value. However, by far the most unique process is the diepoxide rearrangement of epidioxides, providing a beautiful synthetic route to complex organic molecules that are very difficult to synthesize by classical routes. There is little doubt that cyclic peroxides occupy an important place in organic synthesis.

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[1] a) *W. Adam* and *R. Rucktäschel*, J. Amer. Chem. Soc. *93*, 557 (1971); b) *O. L. Chapman, P. J. Wojtkowski, W. Adam, O. Rodriguez*, and *R. Rucktäschel*, *ibid.* *94*, 1365 (1972); c) *W. Adam, J. C. Liu*, and *O. Rodriguez*, J. Org. Chem. *38*, 2269 (1973).

[2] a) *E. Vogel, H.-J. Altenbach*, and *C.-D. Sommerfeld*, Angew. Chem. *84*, 986 (1972); Angew. Chem. internat. Edit. *11*, 939 (1972); b) *C. H. Foster* and *G. H. Berchthold*, J. Amer. Chem. Soc. *94*, 7939 (1972).

[3] *F. D. Greene*, J. Amer. Chem. Soc. *78*, 2246 (1956).

[4] *G. Wittig* and *H. F. Ebel*, Liebigs Ann. Chem. *650*, 20 (1961).

[5] *L. Horner* and *H. Brüggemann*, Liebigs Ann. Chem. *635*, 27 (1960).

[6] *M. Jones, Jr.* and *M. R. DeCamp*, J. Org. Chem. *36*, 1536 (1971).

[7] *V. Dvorák, J. Kolc*, and *J. Michl*, Tetrahedron Lett. *1972*, 3443.

[8] *O. L. Chapman, C. L. McIntosh, J. Pacansky, G. V. Calder*, and *G. Orr*, J. Amer. Chem. Soc. *95*, 4061 (1973).

[9] *M. M. Martin* and *J. M. King*, J. Org. Chem. *38*, 1588 (1973).

[10] *W. Adam* and *G. Santiago Aponte*, J. Amer. Chem. Soc. *93*, 4300 (1971).

[11] a) *W. Adam* and *J. Baeza*, J. C. S. Chem. Comm. *1972*, 103; b) *W. Adam* and *C. Wilkerson*, *ibid.* *1971*, 1569; c) *W. Adam, Y. M. Cheng, C. Wilkerson*, and *W. A. Zaidi*, J. Amer. Chem. Soc. *91*, 1111 (1969); d) *W. Adam* and *Y. M. Cheng*, *ibid.* *91*, 1109 (1969); e) *F. D. Greene, W. Adam*, and *G. A. Knudsen, Jr.*, J. Org. Chem. *31*, 2087 (1966).

[12] *R. Wheland* and *P. D. Bartlett*, J. Amer. Chem. Soc. *92*, 6057 (1970).

[13] *W. Adam* and *R. Rucktäschel*, J. Amer. Chem. 37, 4128 (1972).

[14] a) *P. R. Story, D. P. Denson, C. E. Bishop, B. C. Clark, Jr.*, and *J. G. Farine*, J. Amer. Chem. Soc. *90*, 817 (1968); cf. Chem. Eng. News *46*, No. 6, p. 20 (1968); b) *P. Bush* and *P. R. Story*, Synthesis *1970*, 18; cf. Chem. Eng. News *48*, No. 10, p. 41 (1970); c) *P. R. Story* and *P. Busch*, Advan. Org. Chem. *8*, 67 (1972).

[15] *R. Hiatt* in *D. Swern*: Organic Peroxides. Wiley-Interscience, New York 1971. Vol. 2, p. 856ff.

[16] *R. Kaptein, M. Frater-Schröder*, and *L. J. Oosterhoff*, Chem. Phys. Lett. *12*, 16 (1971).

[17] a) *G. O. Schenck*, Z. Elektrochem. *56*, 855 (1952); b) *C. F. Wilcox, Jr.* and *M. P. Stevens*, J. Amer. Chem. Soc. *84*, 1258 (1962).

[18] a) *C. S. Foote, S. Wexler, W. Ando*, and *R. Higgins*, J. Amer. Chem. Soc. *90*, 975 (1968); b) *R. W. Murray* and *M. L. Kaplan*, *ibid.* *91*, 5358 (1969).

[19] *W. Dilthey, S. Henkels*, and *M. Leonhard*, J. Prakt. Chem. *151*, 97 (1938).

[20] *C. F. H. Allen* and *J. A. van Allan*, J. Org. Chem. *18*, 882 (1953).

[21] a) *W. Adam* and *N. Durán*, J. C. S. Chem. Comm. *1972*, 279; b) J. Org. Chem. *38*, 1434 (1973); c) Tetrahedron Lett. *1972*, 1357.

[22] *E. Bernatek* and *M. Hoatum*, Acta Chem. Scand. *14*, 836 (1960).

[23] a) *P. R. Story, W. H. Morrison, III, T. K. Hall, J.-C. Farine*, and *C. E. Bishop*, Tetrahedron Lett. *1968*, 3791; b) *P. R. Story, T. K. Hall, W. H. Morrison, III.*, and *J.-C. Farine*, *ibid.* *1968*, 5397.

[24] *P. R. Story, W. H. Morrison, III.*, and *J. M. Butler*, J. Amer. Chem. Soc. *91*, 2398 (1969).

[25] a) *R. Criegee*, Chimia *22*, 392 (1968); b) *R. Huber*, Dissertation, Technische Universität Karlsruhe 1970; c) *R. Wolf*, Dissertation, Technische Universität Karlsruhe 1971.

[26] *D. T. Carty*, Tetrahedron Lett. *1969*, 4753.

[27] *G. Maier* and *M. Schneider*, Angew. Chem. *85*, 174 (1973); Angew. Chem. internat. Edit. *12*, 162 (1973).

[28] a) *A. Guyot* and *J. Catel*, Bull. Soc. Chim. Fr. *35*, 1124 (1906); b) *C. Dufraisse* and *S. Ecary*, C. R. Acad. Sci. *223*, 735 (1946); c) *J. R. Scheffler* and *M. D. Ouchi*, Tetrahedron Lett. *1970*, 223.

[29] a) *J. Martel*, C. R. Acad. Sci. *244*, 626 (1957); b) *E. Koch* and *G. O. Schenck*, Chem. Ber. *99*, 1984 (1966); c) *C. S. Foote, M. T. Wuesthoff, S. Wexler, I. G. Burstain, R. Denney, G. O. Schenck*, and *K.-H. Schulte-Elte*, Tetrahedron *23*, 2583 (1967).

[30] *H. H. Wasserman* and *A. R. Doumaux, Jr.*, J. Amer. Chem. Soc. *84*, 4611 (1962).

[31] *T. J. Katz, V. Balogh*, and *J. Schulman*, J. Amer. Chem. Soc. *90*, 734 (1968).

[32] a) *K. R. Kopecky* and *C. Mumford*, Can. J. Chem. *47*, 709 (1969); b) *P. D. Bartlett* and *A. P. Schaap*, J. Amer. Chem. Soc. *92*, 3223 (1970); c) *S. Mazur* and *C. S. Foote*, *ibid.* *92*, 3225 (1970); d) *J. H. Wieringa, J. Strating, H. Wynberg*, and *W. Adam*, Tetrahedron Lett. *1972*, 169.

[33] a) *W. Adam* and *J. C. Liu*, J. Amer. Chem. Soc. *94*, 2894 (1972); b) *W. Adam* and *H.-C. Steinmetzer*, Angew. Chem. *84*, 590 (1972); Angew. Chem. internat. Edit. *11*, 540 (1972).

[34] *M. M. Rauhut*, Accounts Chem. Res. *2*, 80 (1969).

[35] a) *E. H. White, J. Wiecko*, and *D. F. Roswell*, J. Amer. Chem. Soc. *91*, 5794 (1969); b) *E. H. White, J. Wiecko*, and *C. C. Wei*, *ibid.* *92*, 2167 (1970); c) *E. H. White* and *C. C. Wei*, Biochem. Biophys. Res. Commun. *39*, 1219 (1970).

[36] *A. Lamola*, Biochem. Biophys. Res. Commun. *43*, 895 (1971).

[37] *N. J. Turro* and *P. Lechtken*, J. Amer. Chem. Soc. *94*, 2886 (1972).

[38] *N. J. Turro* and *P. Lechtken*, Tetrahedron Lett. *1973*, 565.

[39] *W. H. Richardson, F. C. Montgomery*, and *M. B. Yelvington*, J. Amer. Chem. Soc. *94*, 9277 (1972).

[40] *H. Güsten* and *E. F. Ullman*, J. C. S. Chem. Comm. *1970*, 28.

[41] a) *A. Windaus, W. Bergmann*, and *A. Lüttringhaus*, Liebigs Ann. Chem. *472*, 195 (1929).; b) *E. L. Skan* and *W. Bergmann*, J. Amer. Chem. Soc. *60*, 986 (1938); c) *W. Bergmann, F. Hirschmann*, and *E. L. Skan*, J. Org. Chem. *4*, 29 (1939); d) *C. R. Conca* and *W. Bergmann*, *ibid.* *18*, 1104 (1953).

[42] *G. O. Schenck* and *K. Ziegler*, Naturwissenschaften *32*, 157 (1945).

[43] a) *J. Boche* and *O. Runquist*, J. Org. Chem. *33*, 4285 (1968); b) *K. K. Maheshwari, P. de Mayo*, and *D. Wiegand*, Can. J. Chem. *48*, 3265 (1970).

[44] *C. S. Foote, S. Mazur, P. A. Burns*, and *D. Lerdal*, J. Amer. Chem. Soc. *95*, 586 (1973).

[45] *H. H. Wasserman, J. R. Scheffer*, and *J. L. Cooper*, J. Amer. Chem. Soc. *94*, 4991 (1972).

[46] a) *J. Rigaudy, N. C. Cohen*, and *N. K. Cuong*, C. R. Acad. Sci. *264*, 1851 (1967); b) *J. Rigaudy, C. Deletang, D. Sparfel*, and *N. K. Cuong*, *ibid.* *267*, 1714 (1968); c) *J. Rigaudy, C. Deletang*, and *J. J. Basselier*, *ibid.* *268*, 344 (1969).

[47] *I. Saito, S. Kato*, and *T. Matsuura*, Tetrahedron Lett. *1970*, 239.

[48] *G. W. Grams, K. Eskins*, and *G. E. Inglett*, J. Amer. Chem. Soc. *94*, 866 (1972).

[49] *A. Etienne* and *C. Beauvois*, C. R. Acad Sci. *239*, 64 (1954).

[50] *H. H. Wasserman* and *P. M. Keehn*, J. Amer. Chem. Soc. *88*, 4522 (1966); *94*, 298 (1972).

[51] *J. J. Basselier* and *J. P. LeRoux*, C. R. Acad. Sci. *268*, 970 (1969); Bull. Soc. Chim. Fr. *1971*, 4448.

[52] a) *K. H. Schulte-Elte, B. Willham*, and *G. Ohloff*, Angew. Chem. *81*, 1045 (1969); Angew. Chem. internat. Edit. *8*, 985 (1969); b) *W. R. Adams* and *D. J. Trecker*, Tetrahedron *27*, 763 (1971).

[53] a) *J. J. Basselier*, C. R. Acad. Sci. *258*, 2851 (1969); b) *J. P. LeRoux* and *J. J. Basselier*, *ibid.* *271*, 461 (1970).

[54] *W. Skorianetz, K.-H. Schulte-Elte*, and *G. Ohloff*, Helv. Chim. Acta *54*, 1913 (1971); Angew. Chem. *84*, 311 (1972); Angew. Chem. internat. Edit. *11*, 330 (1972).

[55] *N. Harada, S. Suzuki, H. Uda*, and *H. Ueno*, J. Amer. Chem. Soc. *94*, 1777 (1972).

[56] *E. J. Forbes* and *J. Griffith*, J. Chem. Soc. *C 1968*, 572, 575.

[57] *T. Tezuka, R. Migamoto, T. Mukai, C. Kabuto*, and *Y. Kitahara*, J. Amer. Chem. Soc. *94*, 9280 (1972).

[58] *R. Criegee, P. DeBruyn*, and *G. Lohaus*, Liebigs Ann. Chem. *583*, 19 (1953).

[59] *E. F. Ullman*, J. Amer. Chem. Soc. *86*, 5357 (1964).

[60] *F. Nahavandi, F. Razwara*, and *M. R. Stevens*, Tetrahedron Lett. *1973*, 301.

[61] a) *H. H. Wasserman* and *M. B. Floyd*, Tetrahedron Suppl. *7*, 441 (1966); b) *H. H. Wasserman, F. J. Vinick*, and *Y. C. Chang*, J. Amer. Chem. Soc. *94*, 7180 (1972).

[62] *H. H. Wasserman, A. R. Doumaux*, and *R. E. Davis*, J. Amer. Chem. Soc. *88*, 4517 (1966).

[63] *H. H. Wasserman* and *R. Kitzing*, Tetrahedron Lett. *1969*, 5315.

New synthetic methods (4)

1,3-Anionic Cycloadditions of Organolithium Compounds: An Initial Survey[1]

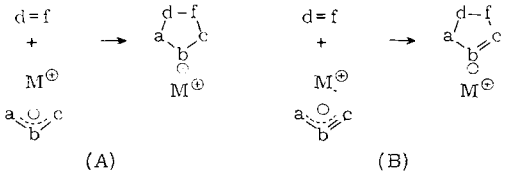
By Thomas Kauffmann[*]

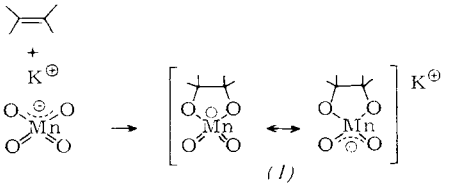
In Memory of Clemens Schöpf

In the field of [3+2]-cycloaddition reactions, 1,3-anionic cycloadditions have now joined 1,3-dipolar cycloadditions as a second reaction type of major general importance. The cycloaddition in question has been found to occur with 2-azaallyllithium compounds, allyllithium compounds (with an electron acceptor located on C^2), and 1,3-diphenylpropargyllithium. Compounds with CC, CN, NN, and CS double bonds and those with CC and CN triple bonds were found to be 1,3-anionophilic. 1,3-Anionic cycloaddition opens new routes to 1-aza-, 1,2-diaza-, 1,3-diaza-, 1,2,4-triaza-, and 1-thia-3-azacyclopentane derivatives, to pyrroles and imidazoles, as well as (and this appears to be of special importance) to cyclopentane derivatives. Currently available data attribute stereospecificity to the 1,3-anionic cycloadditions, which occupy an interesting intermediate position between 1,3-dipolar cycloadditions and transition-metal-catalyzed cyclizations. A two-step mechanism has been demonstrated in one case.

1. Definition and History of Discovery

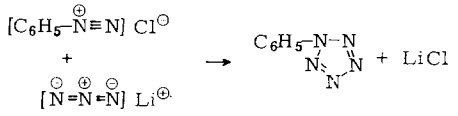
1,3-Anionic cycloadditions[2] are single-step or multiple-step reactions in which "1,3-anions" react with substrates ("1,3-anionophiles") containing a double or a triple bond to yield cycloadducts *via* routes (A) or (B). The reactions differ from the closely related 1,3-dipolar cycloadditions in that the positive charge is separately accommodated at a cation (which may be linked to the anion *via* a partially covalent bond). The first phase of *Baeyer*'s permanganate test, involving the addition of potassium permanganate to a CC double bond with the formation of a cycloadduct of type *(1)*, constitutes a long-known reaction of this kind.



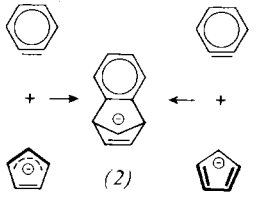


The well known combination of lithium azide with the phenyldiazonium ion to give phenylpentazole[3] is a 1,3-anionic cycloaddition with a cationic 1,3-anionophilic agent.

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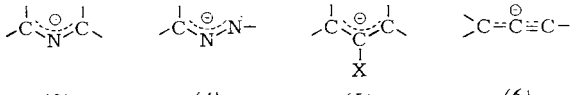


Wittig et al.[4] were able to trap dehydrobenzene in the presence of strong bases by cycloaddition with cyclopentadiene. Since *Ford et al.*[5] have shown that the cyclopentadienyl anion gives an anionic adduct of type *(2)* under such circumstances, the above reactions can therefore also be regarded as 1,3-anionic cycloadditions. However, the following formulas show that they can just as well be regarded as Diels-Alder reactions, since a six-membered ring with an isolated CC-double bond is formed.

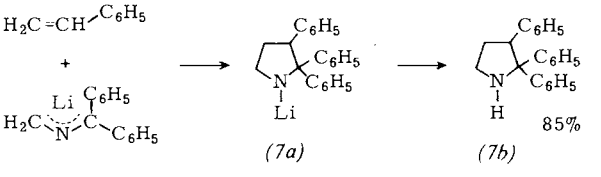


(2)

Such ambiguity is absent from our cycloadditions involving open-chain anions of types *(3)*—*(6)*[6]. The first reaction of this kind, *i.e.* formation of 2,2,3-triphenylpyrrolidine *(7b)* (85%) *via* the intermediate *(7a)*, was observed early in 1970[7, 22].



(3) *(4)* *(5)* *(6)*



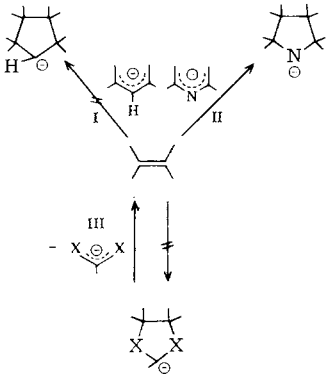
(7a) *(7b)*

2. Stabilization of the Negative Charge in 1,3-Anionic Cycloadditions and Their Reversal

Some remarks on the significance of charge stabilization in 1,3-anionic cycloadditions with organolithium compounds may perhaps facilitate understanding of the subsequent sections.

Like 1,3-dipolar cycloadditions[8], provided that they proceed in concerted fashion (see, however, Sections 3.2.1 and 4.2) the cycloadditions in question are symmetry-dependent [$_\pi 2_s + _\pi 4_s$] processes. The basic reaction of this type was formulated by *Woodward* and *Hoffmann* (reaction I in Scheme 1)[9]. While a reaction conforming exactly to this basic type has not yet been implemented, this has been achieved in the case of analogous cycloadditions of allyl anions[10] with an electron-attracting substituent on the central carbon (Section 4.2). Available information indicates that the heteroallyl anions best suited for 1,3-anionic cycloaddition are the 2-azaallyl anions[10] (cf. Section 3). Characteristically, a relatively electronegative nitrogen located at the center of the heteroallyl system is flanked by two less electronegative carbons. Prior to the cycloaddition the negative charge is largely located at these peripheral carbons; during the reaction (reaction II in Scheme 1) it migrates to the more electronegative central nitrogen. In contrast to the 2-azaallyl anions, heteroallyl anions which contain electronegative atoms in the peripheral positions and a less electronegative atom at the center like the carboxylate ion are unsuitable for cycloaddition; they are readily formed by 1,3-anionic cycloeliminations (reaction III in Scheme 1; see also Section 5). The 1,2-diazaallyl anions occupy an intermediate position: cycloadditions have been observed only with substrates having strained multiple bonds (cf. Section 4.1).

Thus, apart from the reactions with the extremely labile dehydrobenzene, 1,3-anionic cycloadditions only occur where the negative charge is not extensively destabilized.



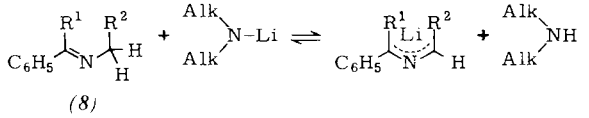
Scheme 1. Charge stabilization as a direction-determining factor. I, II, III, see text. X = O or S.

3. 2-Azaallyllithium Compounds

3.1. Preparation

1-Azaallyllithium compounds are well known as reagents for "directed aldol condensations"[11]. In contrast, the isomeric 2-azaallyllithium compounds had not been described in the literature prior to the beginning of our investigations[12]. We were able to prepare them in solution in the following manner.

Hydrogen-lithium exchange in azomethines (method A): Azomethines of type *(8)* are rapidly lithiated[13] with lithium dialkylamides in ether or THF at −70 to −30 °C to give 2-azaallyllithium compounds. Experience gained so far practically rules out any danger of their undergoing undesirable reactions with the azomethine under these conditions.



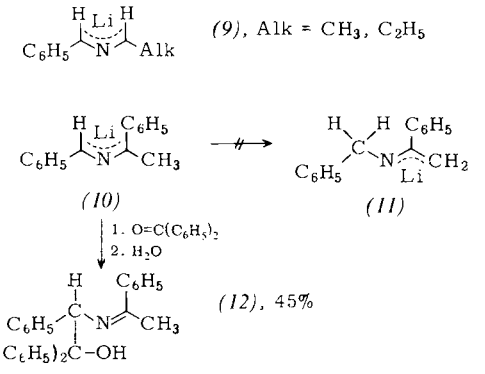
(8)

$R^1 = R^2 = C_6H_5$; $R^1 = C_6H_5$, $R^2 = H$; $R^1 = H$, $R^2 = C_6H_5$

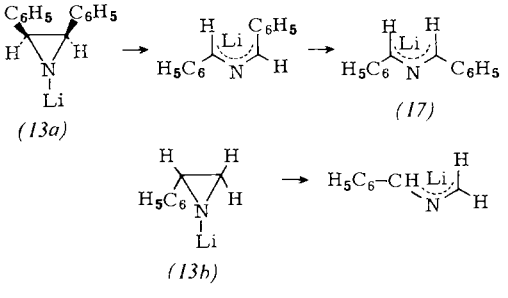
The 2-azaallyllithium solutions thus prepared contain a free secondary amine and its lithium compound owing to equilibration as shown. Consequently, the solutions are unsuitable for reactions with 1,3-anionophilic agents prone to irreversible reaction with amines and lithium amides. With lithium dimeth-

ylamide as the lithiating agent, however, the free amine can be largely evaporated prior to addition of the 1,3-anionophilic agent[14].

Attempted analogous preparation of 1-alkyl-3-phenyl-2-azaallyllithium compounds *(9)* in significant yield failed because the appropriate azomethines could not be metalated[15]. However, compound *(10)* was prepared. Its reaction with benzophenone to yield exclusively *(12)* shows that the isomerization to the 1-azaallyllithium compound *(11)* (this being associated with a gain in charge-stabilizing electronegativity but loss in conjugation energy) occurs at the most to a slight extent[16].



Conrotatory ring opening of N-lithiated aziridines (method B): In this procedure the 2-azaallyllithium compounds are obtained in an amine-free solution. So far, only two examples are known[18,19].



Ring opening of *(13a)* occurs rapidly in THF at 30—40 °C (for detection and configuration of the 2-azaallyllithium compound, see Sections 3.2.1), but that of *(13b)* only proceeds slowly even at 65 °C in the same solvent[19,20].

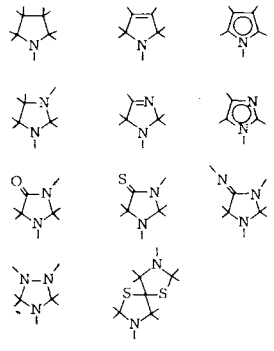
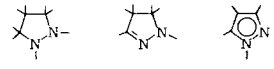
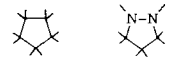
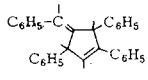
Thermal decomposition of 4-lithio-1,2,4-triazolidines (method C): As shown in Section 5.1, *trans,trans*-1,3-diphenyl-2-azaallyllithium *(17)* is also formed by heating 4-lithio-1,2,3,5-tetraphenyl-1,2,4-triazolidine *(70)*[21]. Other substituted 2-azaallyllithium compounds can probably be obtained similarly.

3.2. Preparative Applications

2-Azaallyllithium compounds can add to unsaturated compounds containing CC, CN, NN, CS, and CO double bonds as well as to those containing CC and CN triple bonds. Whereas addition at the CO double bonds always yields open-chain adducts—at least as the final products (cf. Section 3.2.3)—compounds with other multiple bonds generally give cyclic adducts. The ring systems we have so far obtained by such reactions are listed in Table 1. Information on the individual reactions is presented mainly in Tables 2—8.

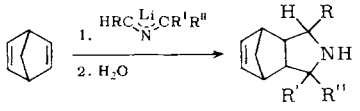
Since the 2-azaallyllithium compounds were always prepared using commercial *n*-butyllithium dissolved in *n*-hexane, the reaction mixtures invariably contained 5—10% of *n*-hexane. The *n*-hexane content is not mentioned below unless it exceeded 10%.

Table 1. Ring systems obtainable by 1,3-anionic cycloadditions of organolithium compounds.

Reactants	Products
2-Azaallyl-Li compounds	
1,2-Diazaallyl-Li compounds	
Allyl-Li compounds	
1,3-Diphenylpropargyllithium	

3.2.1. Reactions with Simple Alkenes

The unstrained isolated CC double bond of cyclohexene does not appear to be attacked by 1,1- or 1,3-diphenyl-2-azaallyllithium. The formation of *(14a)* or *(14b)* from norbornadiene in THF at 20 °C[22,23] shows, on the other hand, that strained isolated double bonds can undergo 1,3-anionic cycloaddition with 2-azaallyllithium compounds. Compounds with an olefinic CC double bond conjugated with an aromatic system (Table 2) are better 1,3-anionophiles. Details are given in Sections 3.2.2 to 3.2.7.



(14a), R = H, R' = R'' = C_6H_5 33%
(14b), R = R' = C_6H_5, R'' = H 35%

Regioselectivity: Although 1,3-dipolar cycloadditions generally proceed as concerted processes, the addition of asymmetrically substituted 1,3-dipoles to asymmetrically substituted multiple bonds usually displays a distinct preference for one of the two orientations[8]. The first 1,3-anionic variant we observed (the reaction between 1,1-diphenyl-2-azaallyllithium and styrene formulated at the outset) has showed that 1,3-anionic cycloadditions can also be markedly regioselective. Of the two possible protonated cycloadducts 2,2,3-triphenyl- *(7b)* and 2,2,4-triphenylpyrrolidine, the isomer obtained

Table 2. Cycloaddition of 2-azaallyllithium compounds to simple alkenes.

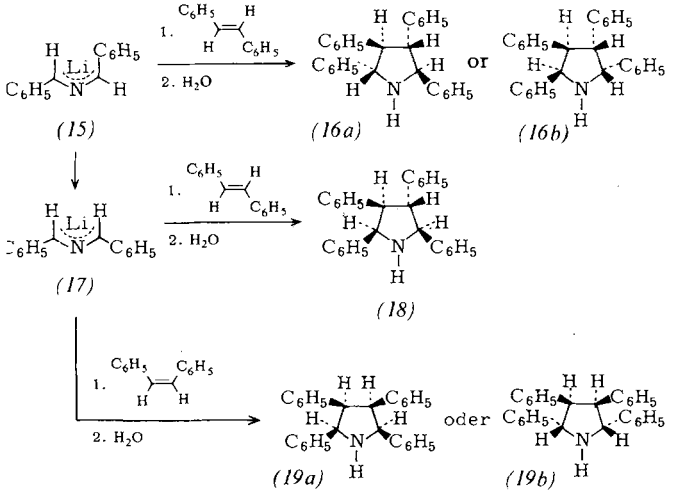
2-Azaallyl-Li compounds	1,3-Anionophile	T [°C]	t [h]	Products	Yield [%]	Ref.
1,1-Diphenyl-	Styrene	20 [a]	18	2,2,3-Triphenylpyrrolidine *(7b)*	85	[7, 22]
	4-Methoxystyrene	20 [a]	18	3-(*p*-Methoxyphenyl)-2,2-diphenylpyrrolidine	58	[22]
	β-Methylstyrene	20 [a]	18	4-Methyl-2,2,3-triphenylpyrrolidine	24	[22]
1,3-Diphenyl-	Styrene	0 [b]	8	2,3,5-Triphenylpyrrolidine	75	[7, 16]
	trans-Stilbene	0 [b]	24	2,3,4,5-Tetraphenylpyrrolidine *(18)*	83	[7, 16, 25]
	cis-Stilbene	0 [b]	24	2,3,4,5-Tetraphenylpyrrolidine *(19a)* or *(19b)*	21	[16, 25]
	1,2-Bis(2-pyridyl)ethylene	50 [a]	2.5	2,5-Diphenyl-3,4-bis(2-pyridyl)pyrrolidine	73	[23]
	Acenaphthylene	0 [b]	24	7,9-Diphenyl-7,8,9,9a-tetrahydro-6b*H*-acenaphtho-[1,2-*c*]pyrrole *(22a)* and *(23a)*	40 + 40	[16, 25]

[a] In THF.
[b] In THF/ether (10 : 1).

mainly or exclusively was the sterically less favorable one *(7b)* (85% yield). A distinct regioselectivity of this type has also been observed[2] in cycloadditions of 2-azaallyllithiums to 1,3-dienes (Table 3).

Stereospecificity: The 1,3-anionic cycloadditions investigated here proved to be stereospecific. The best studied reaction is that of 1,3-diphenyl-2-azaallyllithium with *trans*- and *cis*-stilbene. According to the principle of conservation of orbital symmetry[9] thermal opening of the ring of *N*-lithio-*cis*-2,3-diphenylaziridine *(13a)* would give rise to *cis,trans*-1,3-diphenyl-2-azaallyllithium *(15)* in a conrotatory process. Compound *(15)* could be trapped by conducting the ring-opening process (at 40—60 °C) in the presence of 1 mol of *trans*-stilbene. The 2,3,4,5-tetraphenylpyrrolidine having structure *(16a)* or *(16b)* was formed in a 73% yield, *i.e.* a cycloadduct with the two phenyl residues "inherited" from the 2-azaallyl group in the *trans*-position[18].

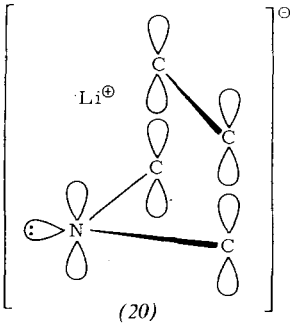
The *cis,trans* compound *(15)* is unstable, and rapidly rearranges to the more stable *trans,trans* compound *(17)*[18, 24].



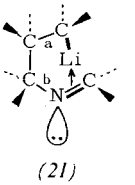
(15) *(16a)* *(16b)* *(17)* *(18)* *(19a)* *(19b)*

This reacts in THF at 0 °C with *trans*-stilbene to yield exclusively *(18)* (83% yield), and with *cis*-stilbene at 0 °C to give a product of the constitution *(19a)* or *(19b)* (21% yield). The products of *(17)* thus have the *cis*-configuration in that part originating from the 2-azaallyl and the configuration in the alkene part is retained. The pyrrolidines obtained from *trans*- and *cis*-stilbene exhibited no detectable mutual contamination. Hence, these cycloadditions are stereospecific with respect to the alkene and the 2-azaallyl components (*cis* addition in each case). The cycloaddition of *(17)* to acenaphthylene is also a purely *cis* addition[25].

These findings can be most readily interpreted in terms of symmetry-dependent single-step $[_\pi 4_s + _\pi 2_s]$-cycloaddition processes. Since the 2-azaallyl anions resemble 1,3-dipolar substances in their orbital scheme (*e.g.* azomethine ylides), the MO considerations[26] pertinent to 1,3-dipolar cycloadditions can be extended to the reactions of 2-azaallyl anions. Provided they are one-step processes, these reactions should therefore proceed *via* a "two-plane orientation complex" *(20)*.



(20)



(21)

However, the observed stereospecificity can also be explained in terms of a two-step process with an intermediate of type *(21)*, in which rotation about the *a*- and *b*-axes is blocked by coordination to the CN double bond or to the nitrogen.

A two-step 1,3-anionic cycloaddition is described in Section 4.2.

In the case of reaction *(17)* → *(18)* the fact that the stereospecificity of this cycloaddition is not in the least impaired (the yield is also virtually unaffected)[21] by the addition of tetramethylethylenediamine, a good complexing agent, may constitute an argument against an intermediate *(21)*.

endo-exo-Isomeric cycloadducts: According to Table 2, the action of 1,3-diphenyl-2-azaallyllithium in THF at 0 °C on acenaphthylene gives rise to two isomeric cycloadducts in approximately equal amounts. By analogy with the structure determinations on *N*-phenylpyrrolidines[27], on the basis of ^{1}H-NMR spectra the *endo*-structure *(22a)* (weaker shielding of the pyrrolidine protons) can be assigned to the higher-melting isomer (m.p. 194 °C), and consequently the *exo*-structure *(23a)* to the lower-melting isomer (m.p. 176 °C)[19, 28].

The lithium compound *(22b)* obtained from *(22a)* by the action of *n*-butyllithium at 0 °C is stable in THF at this temperature, but at 40—50 °C it rearranges quantitatively within 1 h to the thermodynamically more stable *exo*-isomer *(23b)*. There is hardly any doubt that this isomerization proceeds by the formulated cycloelimination-cycloaddition mechanism, especially as acenaphthylene was detectable in small amounts in the reaction mixture.

ing to *(25)*, did not take place when instead of the 2-azaallyllithium compound the corresponding azomethine *(46)* was used in the presence of catalytic amounts of lithium diisopropylamide (cf. Section 3.2.7 and Table 8), which can be plausibly explained by more rapid protonation of the anionic cycloadduct (lithium compound of *(24)*) by the azomethine (*N*-benzylidenebenzylamine) abundantly present in the reaction mixture.

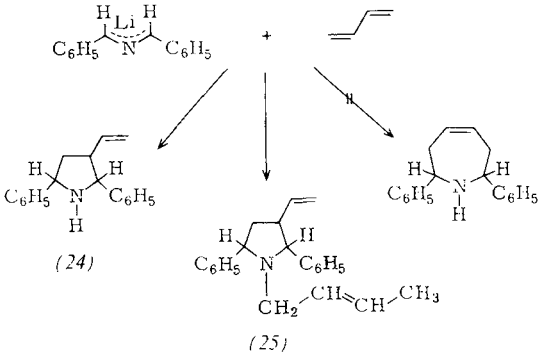
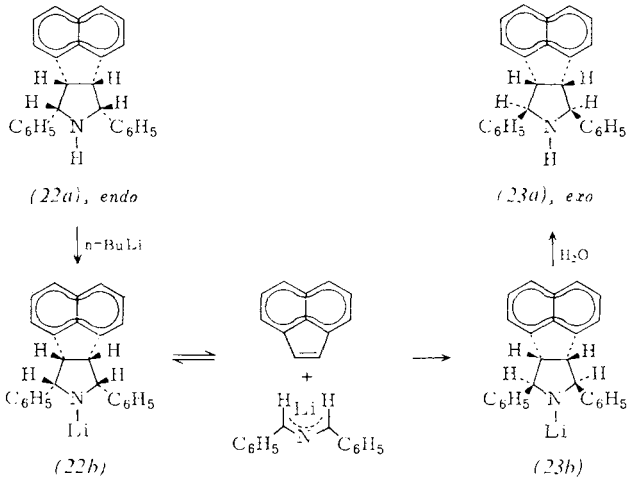


Table 3. Cycloaddition of 2-azaallyllithium compounds to 1,3-dienes in THF at 20 °C (reaction time 16 h) [2, 29].

2-Azaallyl-Li compound	1,3-Anionophile	Product	Yield [%]
1,3-Diphenyl-	1,3-Butadiene	2,5-Diphenyl-3-vinylpyrrolidine *(24)*	36
		1-(2-Butenyl)-2,5-diphenyl-3-vinylpyrrolidine *(25)*	47
	Isoprene	3-(1-Methylvinyl)-2,5-diphenylpyrrolidine	92
1,1-Diphenyl-	1,3-Butadiene	2,2-Diphenyl-3-vinylpyrrolidine	91
	Isoprene	3-(1-Methylvinyl)-2,2-diphenylpyrrolidine	35
		3-Methyl-2,2-diphenyl-3-vinylpyrrolidine	13
1,1,3-Triphenyl- [a]	1,3-Butadiene	2,2,5-Triphenyl-3-vinylpyrrolidine	35

[a] In this experiment, the temperature had to be increased to 66 °C.



3.2.2. Reactions with 1,3-Dienes

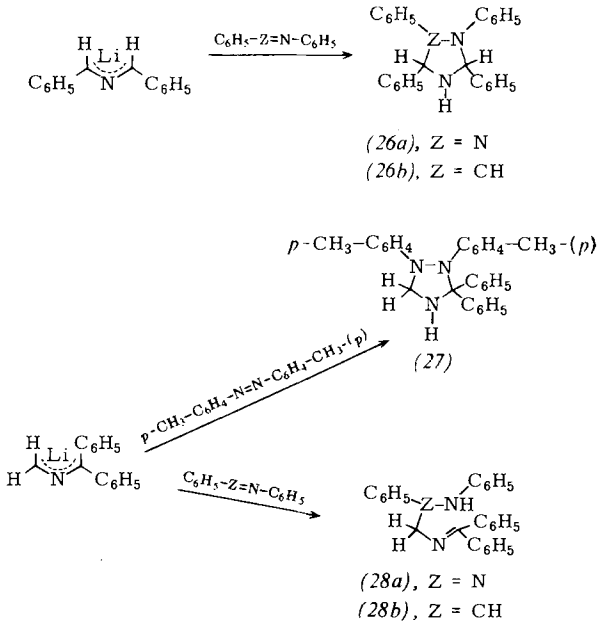
1,3-Dienes are also convenient 1,3-anionophiles (Tables 3 and 8)[2, 14, 29]. They react with 2-azaallyllithiums to give, apparently exclusively, five-membered cycloadducts; seven-membered ones could not be isolated. In one case the cycloaddition was associated with a secondary reaction. This reaction, leading to *(25)*, did not take place when instead of the 2-azaallyllithium compound the corresponding azomethine *(46)* was used in the presence of catalytic amounts of lithium diisopropylamide (cf. Section 3.2.7 and Table 8), which can be plausibly explained by more rapid protonation of the anionic cycloadduct (lithium compound of *(24)*) by the azomethine (*N*-benzylidenebenzylamine) abundantly present in the reaction mixture.

Table 3 shows that the 1,3- and 1,1-diphenyl-2-azaallyllithium compounds expectedly undergo cycloaddition preferably at the electron-depleted and sterically more readily accessible double bond of isoprene. The 1,3-diphenyl compound shows by far the higher selectivity.

3.2.3. Reactions with Azo Compounds and Azomethines

1,3-Diphenyl-2-azaallyllithium undergoes cycloaddition to the aromatic azo compounds and azomethines listed in Table 4 with the formation of 1,2,4-triazolidines or imidazolidines (*e.g. (26a)* and *(26b)*)[30]. In contrast, no reaction was observed[22, 31] with 4-dimethylaminoazobenzene, 2,2'-azonaphthalene, and 3,3'-azoquinoline under the corresponding conditions. The stereochemistry of the chirality centers of the products has yet to be elucidated.

In contrast, 1,1-diphenyl-2-azaallyllithium, which is generally more prone to form open-chain adducts than the 1,3-isomer (cf. Section 3.2.6), gives the expected cycloadduct *(27)* only with *p,p'*-azotoluene. With azobenzene and azomethines, open-chain adducts of the type *(28a)* or *(28b)* are formed, contrary to previous assumptions based on an erroneous interpretation of the spectra[30, 32].



(26a), Z = N
(26b), Z = CH

(27)

(28a), Z = N
(28b), Z = CH

Table 5. Products of the reactions between 1,1-diphenyl-2-azaallyllithium and ketones, and the decomposition products obtained [16].

RR'C=O added	Yield [%] of: (29)	(30) [a]	(31) [b]
$R=R'=C_6H_5$	42	76	42
$R=C_6H_5$, $R'=p$-Tolyl	32	78	56
$R=CH_3$, $R'=C_6H_5$	32	48	[c]
Fluorenone	52	80	51

[a] Obtained by heating the azomethine with 2 N HCl to 80 °C and liberating the base.
[b] Obtained by dehydration with thionyl chloride/pyridine.
[c] Preparation not investigated.

the 2-azabutadienes (31)[17]. Information on the relevant reactions is given in Table 5. On attempted addition of 1,3-diphenyl-2-azaallyllithium to benzophenone the ketone was recovered largely unaltered[21].

In the benzene/hexamethylphosphoric triamide (1:1) solvent system the yield of (29) $R=R'=C_6H_5$ increased from 42 to 62%; furthermore, the adducts of benzaldehyde and isobutyraldehyde analogous to (29) were prepared in *ca.* 60% yield[35]. The same benzaldehyde adduct was also formed in THF containing diisopropylamine (40%)[21], whereas the action of 1,2-diphenyl-2-azaallyllithium on benzaldehyde and other aldehydes in amine-free THF leads to products [structure (33)?] which regenerate the aldehyde on addition of water[36].

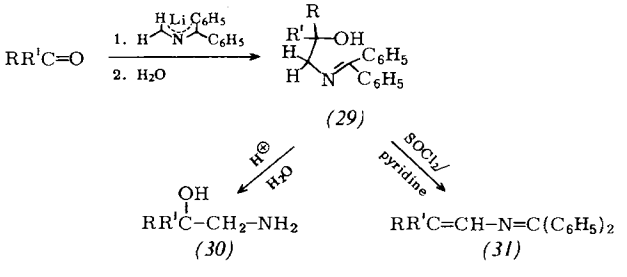
Table 4. Cycloadditions and additions of 2-azaallyllithium compounds to azocompounds and azomethines [a].

2-Azaallyl-Li compound	1,3-Anionophile	Product	Yield [%]	Ref.
1,3-Diphenyl-	Azobenzene [b]	1,2,3,5-Tetraphenyl-1,2,4-triazolidine (26a)	73	[21, 22, 30]
1,1-Diphenyl-	Azobenzene	*N*-(*N*-Diphenylmethylene)-aminomethyl-hydrazobenzene (28a)	43	[21, 22, 30]
	p,p'-Azotoluene [b, c]	3,3-Diphenyl-1,2-bis(*p*-tolyl)-1,2,4-triazolidine (27)	58	[30, 31]
1,3-Diphenyl-	*N*-Benzylidene-aniline [d]	2,3,4,5-Tetraphenyl-imidazolidine (26b)	52	[22, 30]
	N-(2-Pyridylmethylene)-aniline [d]	1,2,4-Triphenyl-5-(2-pyridyl)imidazolidine	54	[22, 30]
1,1-Diphenyl-	*N*-Benzylidene-aniline [b]	2-(Diphenylmethyleneamino)-1-phenylethylaniline (28b)	43	[21, 22, 30]
	N-(2-Pyridylmethylene)-aniline [b]	2-(Diphenylmethyleneamino)-1-(2-pyridyl)ethylaniline	41	[21, 30, 33]

[a] In general the compound was lithiated for 4—5 h at −60 °C, the substrate was added at the same temperature, and the mixture was maintained for several hours at 20 °C. [b] In THF/*n*-hexane (5:1). [c] Heated for 3 h at 65 °C. [d] In THF/ether (9:1).

3.2.4. Reactions with Ketones and Aldehydes

Reactions of 1,1-diphenyl-2-azaallyllithium with ketones and then with water did not yield cyclic products but open-chain compounds of type (29)[13, 17]. It is still unclear whether the reactions involve cyclic intermediates of type (32). The iminomethylation products (29) obtained from 1,1-diphenyl-2-azaallyllithium are of preparative interest since they give rise to β-amino alcohols (30) on hydrolytic cleavage with acids. Both reaction steps thus permit nucleophilic aminomethylation of ketones[13, 34]. Moreover, dehydration of compounds (29) with thionyl chloride/pyridine provides an entry to the hitherto relatively inaccessible class of compounds,



(29)

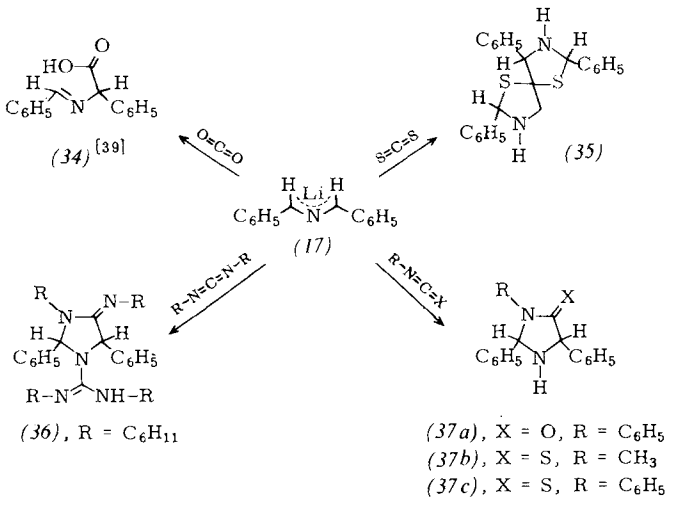
(30)

(31)

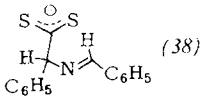
3.2.5. Reactions with Heterocumulenes

The preparation of *trans,trans*-1,3-diphenyl-2-azaallyllithium (17) in solutions containing neither amine nor lithium amide, mentioned in Section 3.1 and 3.2.1, permitted investigations on the behavior of this organolithium compound towards those substrates which, like the oxiranes[37] or heterocumulenes, react irreversibly with amines and lithium amides. Reaction with the heterocumulenes listed in Table 6 and subsequent

hydrolysis with water afforded compounds *(34)*—*(37)*[38] Just these few examples reveal four reaction types.

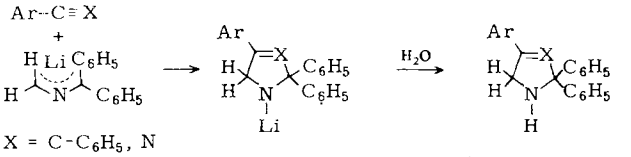


The reaction *(17)* → *(35)* is the first 1,3-anionic cycloaddition to a CS double bond. Attempts to prepare the monocycloadduct of carbon disulfide were unsuccessful. As in the 1,3-dipolar cycloaddition of diphenylnitrilimine to carbon disulfide[8], the first step is clearly slower than the second. This is understandable if the first step of the cycloaddition is assumed to involve a transition state similar to *(38)* with good stabilization of the negative charge.

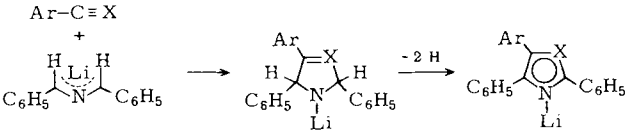

(38)

The relatively high yield of *(36)* (60 %) permits the conclusion that the dicyclohexylcarbodiimide, although added slowly to the solution of *(17)*, was abundantly available to the anionic cycloadduct for further reaction. Thus the cycloaddition step is again slower than the secondary reaction. Apart from the imidazolidine derivatives *(37)*, no other products could be isolated, implying that the cycloaddition to heterocumulenes with two different double bonds occurs exclusively or predominantly at the CN double bond[40]. Since only one diastereomeric form can be isolated in each case, despite careful chromatographic work-up, all cycloadditions to heterocumulenes are probably stereospecific.

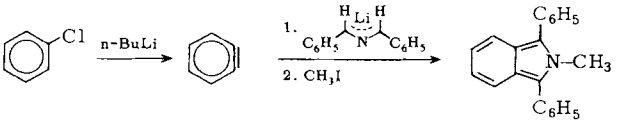
additions, however, limitations appear to be set in this respect by the CH-acidity of many alkynes and nitriles. Thus, it proved impossible, or virtually impossible, to effect cycloaddition of 1,3-diphenyl-2-azaallyllithium to phenylacetylene, 1-phenylpropyne, or aliphatic nitriles (cf. Table 7), which might be due to deactivation of the reagent and substrate by transmetalation. Diphenylacetylene[7] (other non-CH-acid alkynes have still not been tried) and aromatic nitriles nevertheless proved to be 1,3-anionophiles useful for preparative purposes.



Pyrrolines and imidazolines are anticipated as products of the cycloaddition of 2-azaallyllithium compounds to alkynes and nitriles, if side reactions are neglected. The ring systems in question were obtained in the form of the compounds *(39a)* and *(39b)* on use of 1,1-diphenyl-2-azaallyllithium[42].



On the other hand, the corresponding cycloadditions of 1,3-diphenyl-2-azaallyllithium were followed by loss of 2 H atoms, so that pyrroles and imidazoles were formed. This aromatization is presumably initiated by elimination of hydride from *(40)* and concluded by a deprotonation[42].



Stabilization of the primary cycloadduct by loss of hydrogen was also found to occur in the reaction of 1,3-diphenyl-2-azaallyllithium with dehydrobenzene in THF at 20 °C and then with methyl iodide, to give *(41)*[43,44].

Table 6. Cycloaddition and addition of *trans,trans*-1,3-diphenyl-2-azaallyllithium *(17)* to heterocumulenes in THF [38].

	Product	*T* [°C]	*t* [a] [min]	Yield [%]	Ref.
(34)	2-(*N*-Benzylideneamino)phenylacetic acid	−60	60	*ca.* 50	[41]
(35)	2,4,7,9-Tetraphenyl-1,6-dithia-3,8-diazaspiro[4.4]nonane	−40	3 (!)	31	[14]
(36)	3-Cyclohexyl-4-cyclohexylimino-1-(*N,N'*-dicyclohexylamidino)-2,5-diphenylimidazolidine	22 [b]	30	60	[14]
(37a)	2,3,5-Triphenylimidazolidin-4-one	−40	30	55	[14]
(37b)	3-Methyl-2,5-diphenylimidazolidine-4-thione	−40	30	46	[14]
(37c)	2,3,5-Triphenylimidazolidine-4-thione	−40	30	59	[14]

[a] Time of dropwise addition (≈2 min) not included.
[b] No reaction at −40 °C.

3.2.6. Reactions with Alkynes and Nitriles

Alkynes and nitriles of all types are suitable substrates for 1,3-dipolar cycloadditions[8]. In the case of 1,3-anionic cycloadditions, however, limitations appear to be set in this respect by the CH-acidity of many alkynes and nitriles. Thus, it proved impossible, or virtually impossible, to effect cycloaddition of 1,3-diphenyl-2-azaallyllithium to phenylacetylene, 1-phenylpropyne, or aliphatic nitriles (cf. Table 7), which might be due to deactivation of the reagent and substrate by transmetalation. Diphenylacetylene[7] (other non-CH-acid alkynes have still not been tried) and aromatic nitriles nevertheless proved to be 1,3-anionophiles useful for preparative purposes.

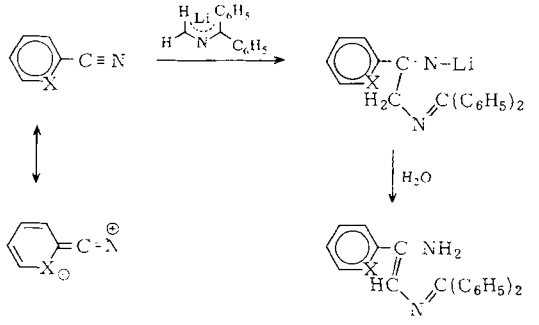
According to Table 7, 1,1-diphenyl-2-azaallyllithium reacts with *m*-tolunitrile and with *p*-methoxybenzonitrile to yield cycloadducts. The corresponding reactions with benzonitrile and pyridine-2-carbonitrile were, however, found to lead to the open-chain enamines *(42)*[42]. Therefore, in view of the

Table 7. Cycloaddition of 2-azaallyllithium compounds to organic compounds containing triple bonds [a].

2-Azaallyl-Li compounds	Substrate	Product [d]	Yield [%]	Ref.
1,3-Diphenyl-	Diphenylacetylene [b]	2,3,4,5-Tetraphenylpyrrole	73	[7, 17]
1,1-Diphenyl-	Diphenylacetylene [b]	2,2,3,4-Tetraphenyl-3-pyrroline	43	[7, 22]
1,3-Diphenyl-	Benzonitrile [c]	2,4,5-Triphenylimidazole	52	[17, 19, 42]
	p-Tolunitrile [c]	2,5-Diphenyl-4-(*p*-tolyl)imidazole	52	[17, 19, 42]
	m-Tolunitrile [c]	2,5-Diphenyl-4-(*m*-tolyl)imidazole	50	[42, 45]
	Pyridine-3-carbonitrile [c]	2,5-Diphenyl-4-(3-pyridyl)imidazole	47	[42, 45]
	Butyronitrile [c]	2,5-Diphenyl-4-propylimidazole	1	[42, 45]
1,1-Diphenyl-	*m*-Tolunitrile [c]	2,2-Diphenyl-4-(*m*-tolyl)-3-imidazoline	31	[21, 42]
	p-Methoxybenzonitrile [c]	2,2-Diphenyl-4-(*p*-methoxyphenyl)-3-imidazoline	47	[21, 42]
	p-Dimethylaminobenzonitrile [c]	2,2-Diphenyl-4-(*p*-dimethylaminophenyl)-3-imidazoline	42	[21, 42]
1,1,3-Triphenyl-	Benzonitrile [c]	2,4,5,5-Tetraphenyl-3-imidazoline	10	[42, 45]

[a] As a rule reacted for 12—18 h at ≈20 °C.
[b] In THF/ether (10:1).
[c] In THF.
[d] The imidazoles are named as if only the nitrogen arising from azaallyl were protonated.

finding that cycloaddition to the nitrile group occurs only in the presence of electron-supplying substituents on the phenyl nucleus of the aromatic nitriles, a relatively high electron density at the nitrile nitrogen is clearly necessary for closing the CN linkage.

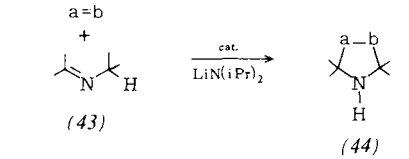


(42), X = CH, N

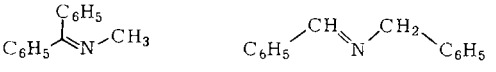
3.2.7. Cycloadditions with CH-Acid Azomethines and Catalytic Quantities of Lithium Diisopropylamide

It is of interest whether the cycloadduct of a 2-azaallyllithium compound and a 1,3-anionophile is able to lithiate CH-acid azomethines. Should this be the case, then in accordance with the scheme *(43)* → *(44)*, 1,3-anionic cycloadditions would be possible with catalytic amounts of a lithium amide, *e.g.* lithium diisopropylamide. A series of experiments with azomethines *(45)* and *(46)*, the results of which are presented in Table 8, corroborates this approach[114].

Whereas, for unknown reasons, the use of *(45)* produced satisfactory results in only two cases, the yields obtained with *(46)* were generally good (Table 8). Alkenes with an extended



(43) *(44)*



(45) *(46)*

π-electron system (styrene, *trans*-stilbene) reacted significantly more rapidly than 1,3-butadiene or isoprene. This cannot be accounted for by basicity differences between the *N*-lithiopyrrolidines formed in the course of the cycloaddition, but must be ascribed to differences in 1,3-anionophilic strength of the alkenes. This conclusion is supported by the occurrence of only one cycloadduct. If lithiation were rate-determining, then not only the *trans,trans*-form *(17)* but also the *cis-trans*-form *(15)* of 1,3-diphenyl-2-azaallyllithium, which is likewise formed (cf. ref. [24]) during the lithiation of the azomethine *(46)*, would be trapped. Thus it appears that the latter compound rearranges completely to the *trans,trans*-form *(17)*, which is stable at room temperature, before cycloaddition occurs.

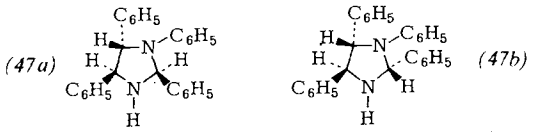
On the other hand, an analogous reaction of *(46)* with *N*-benzylideneaniline gives rise to two isomeric cycloadducts (m. p. 115—117 °C, 44% yield and m.p. 171 °C, 19% yield), the lower-melting isomer being identical with the 2,3,4,5-tetraphenylimidazoline *(26b)* listed in Table 4. The formation of two isomers and the low reaction rate, despite the relatively high 1,3-anionophilicity[46] of *N*-benzylideneaniline, suggest

Table 8. Reaction of *N*-(diphenylmethylene)methylamine *(45)* or *N*-benzylidenebenzylamine *(46)* with unsaturated compounds in the presence of *catalytic amounts* (0.02 mole) of lithium diisopropylamide in THF at 22 °C [14].

1,3-Anionophile	*t* [h]	Isolated reaction products	
		reaction with *(45)*	reaction with *(46)*
1,3-Butadiene	16 and 5	2,2-Diphenyl-3-vinylpyrrolidine (73 %)	2,5-Diphenyl-3-pyrrolidine (95 %)
Isoprene	26 and 2	3-(1-Methylvinyl)-2,2-diphenylpyrrolidine (16 %) 3-Methyl-2,2-diphenyl-3-vinylpyrrolidine (7 %)	3-(1-Methylvinyl)-2,5-diphenylpyrrolidine (90 %)
Styrene	16 and 0.5	[a]	2,3,5-Triphenylpyrrolidine (88 %)
trans-Stilbene	28 and 0.1	[a]	2,3,4,5-Tetraphenylpyrrolidine (92 %)
N-Benzylideneaniline	16 and 18	[a]	1,2,4,5-Tetraphenylimidazoles (2 isomers, 44 and 19 %)
Azobenzene	0.3 and 0.2	[a]	[a]

[a] No detectable reaction product.

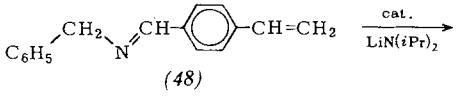
that in this case the lithiation step and not the cycloaddition step is rate determining, and both *trans,trans (17)* and *cis,trans*-1,3-diphenyl-2-azaallyllithium *(15)* consequently participate in cycloaddition. The configurations of the two isomers could not be established by spectroscopy. However, it seems reasonable to assume that the main product derives from *(17)* and therefore has configuration *(47a)*, implying configuration *(47b)* for the other isomer.



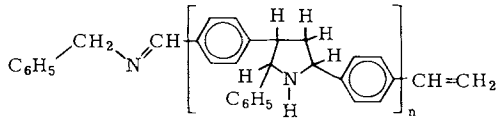
(47a) *(47b)*

The interesting suppression of a side reaction when the reaction of 1,3-butadiene with *(46)* is performed in the presence of catalytic amounts of lithium diisopropylamide, instead of with 1,3-diphenyl-2-azaallyllithium, has already been mentioned in Section 3.2.2.

A catalytic amount of the deprotonating base also suffices in the reaction *(48)* → *(49)* (in THF at 20—30 °C)—a novel and presumably stereospecific "ring-forming polymerization"[47]. The colorless, glasshard polymer has a molecular weight of 7500—8000, and thus contains an average of 35—40 monomer units. Since many compounds are conceivable which contain a 1,3-anionophilic group and a potential 1,3-anionic group like *(48)*, numerous analogous 1,3-anionic polycycloadditions should be possible.



(48)



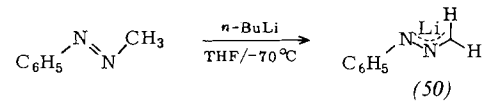
(49)

4. Other Organolithium Compounds Capable of 1,3-Anionic Cycloaddition

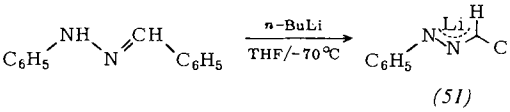
4.1. 1,2-Diazaallyllithium Compounds

For reasons given in Section 2, 1,2-diazaallyllithium compounds were expected to be less inclined to undergo 1,3-anionic cycloaddition than 2-azaallyllithiums. This has been confirmed. 1-Phenyl-1,2-diazaallyllithium *(50)*[48,49] and 1,3-diphenyl-1,2-diazaallyllithium *(51)*[49,50] were prepared in solution in the specified manner (yield 90—100 %). On reaction of *(50)* with carbonyl compounds the phenylhydrazones of α-hydroxyaldehydes and α-hydroxyketones were formed in average to good yields[49,51].

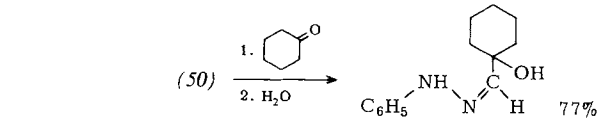
Compound *(50)* reacted with acenaphthylene in THF at 25 °C to give the cycloadduct *(52a)*, which afforded the pyrazolidine *(52b)* (32 %) or the pyrazoline *(53)* (27 %)[49,50], respectively, on addition of water or ethyl bromide. Compound *(52a)*, prepared independently from *(52b)* with *n*-butyllithium, undergoes cycloelimination in THF above 20 °C; after 15 h at 40 °C and hydrolysis with water, 23 % of acenaphthylene and some benzeneazomethane (as one of the hydrolysis products of *(50)*) could be detected[43]. The cycloaddition observed is thus reversible.

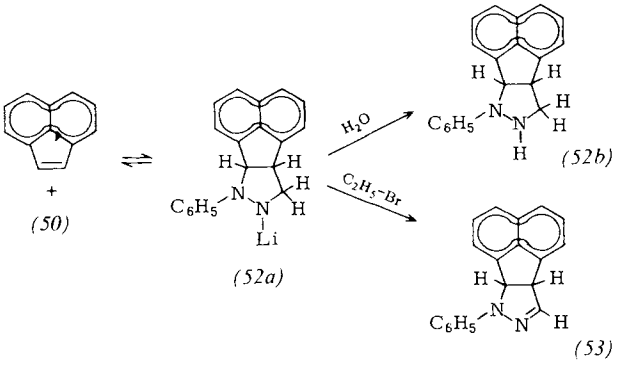


(50)



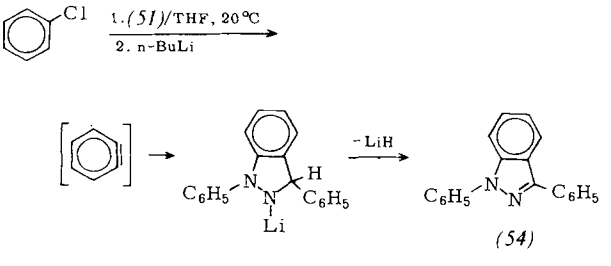
(51)





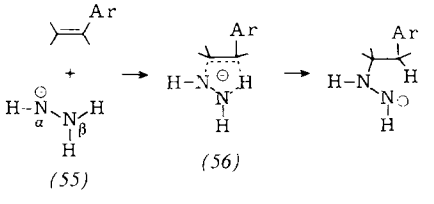
(52a) *(52b)* *(53)*

An analogous cycloaddition of *(51)* to acenaphthylene could not be performed; however, success was achieved in cycloaddition to the more reactive dehydrobenzene, whose preparation from chlorobenzene required addition of *n*-butyllithium. Spontaneous loss of hydride from the cycloadduct led to 1,3-diphenylindazole *(54)* (10 %)[43].



(54)

Attempted cycloaddition of *(50)* and *(51)* to styrene, *trans*-stilbene, or tolane, *i.e.* substrates which, in contrast to acenaphthylene and dehydrobenzene, contain no strained multiple bond, was unsuccessful[50].

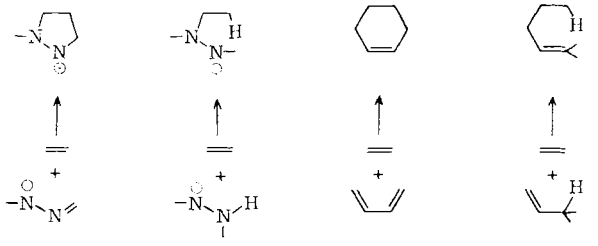


(55) *(56)*

The hydrazide ion *(55)* adds surprisingly easily to multiple bonds[51]. Such marked ability to undergo addition is also observed in the case of the β-monomethylhydrazide ion, but

disappears on replacement of the second H atom on N^{β} by a methyl group. It is therefore assumed that the addition of the hydrazide ion proceeds *via* the cyclic transition state *(56)* with participation of a hydrogen atom[51].

In this connection it is of interest that the addition of hydrazide ion is related to 1,3-anionic cycloaddition in the same way as the "ene reaction" to the Diels-Alder reaction (Scheme 2). In all these four types of reaction, a "quasi-aromatic" transition state[52] is possible.

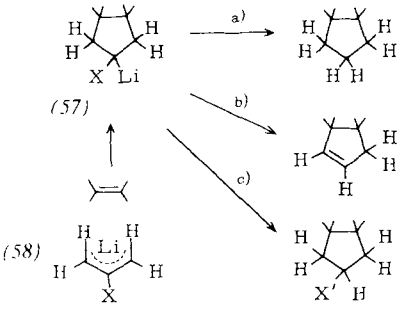


Scheme 2. Comparison of 1,3-anionic cycloaddition of a 1,2-diazaallyl anion with addition of a hydrazide ion, and of the Diels-Alder reaction with the "ene" reaction.

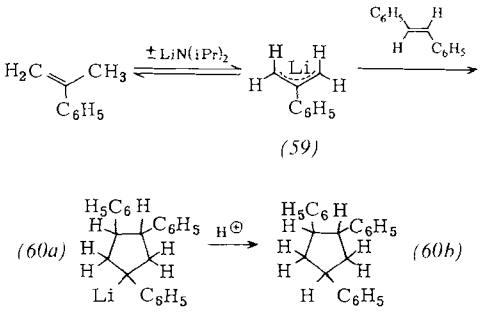
4.2. Allyllithium Compounds

The importance of the Diels-Alder reaction is principally that it provides a convenient way of synthesizing six-membered carbocyclic compounds. A comparably favorable method of preparing five-membered *carbocyclic* compounds would be valuable. The "1,3-dipolar cycloaddition" type of reaction, otherwise so versatile, fails in this respect; as far as we know, only *heterocyclic* compounds could hitherto be synthesized in this way. In contrast, 1,3-anionic cycloadditions are also suitable for the synthesis of carbocyclic compounds[53, 55] and could therefore close a wide gap in the available preparative techniques.

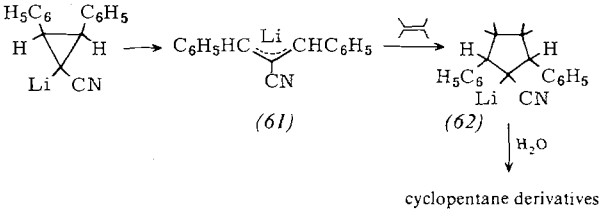
According to the available data, allyllithium compounds undergo cycloaddition to CC double bonds only in cases where an electron-attracting substituent is present on C^2 of the allyl system[14, 54]. A cycloaddition of this kind would only acquire general preparative importance if this substituent [X in *(57)*] could be (a) easily removed by reduction, (b) eliminated together with an α-hydrogen, or (c) exchanged for other substituents after completion of the cycloaddition process. So far this objective has not been achieved.



An allyllithium compound of apparently suitable kind *(58)*, but with substituents not readily removable after the cycloaddition, is 2-phenylallyllithium *(59)*, formed gradually when α-methylstyrene in THF is subjected to the action of lithium diisopropylamide. Reaction of *(59)* with *trans*-stilbene gives the cycloadduct *(60a)*; after addition of water, the cyclopentane derivative *(60b)* could be isolated (41% yield after 130 h at 45 °C)[53, 55].



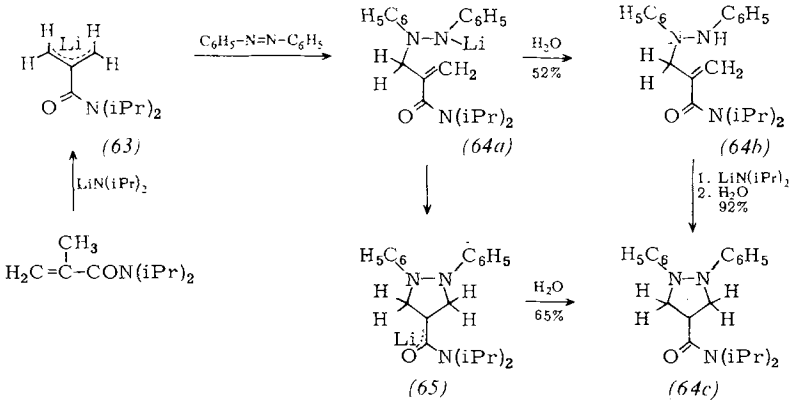
Following the publication of this synthesis, analogous cycloaddition reactions *(61)* → *(62)* were reported, in which the nitrile group effects charge stabilization in the cycloadduct (18—69% yield). Styrene, *trans*-stilbene, 1,1-diphenylethylene, and acenaphthylene served as 1,3-anionophiles; the organolithium compounds *(61)* and *(62)* were unambiguously detected[56].



The stereochemistry at the chirality centers of cyclopentane derivatives produced by 1,3-anionic cycloaddition have still not been fully elucidated.

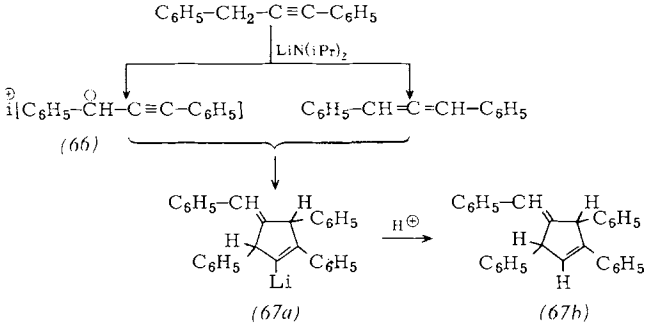
Only the *trans,trans* form of 1,3-diphenyl-2-cyanoallyllithium *(61)* undergoes cycloaddition to activated alkenes, but not the *cis,trans* form[57]. Correspondingly, in spite of the presence of an electron-attracting group at C^2, 1,3-diphenyl-2-(2-pyridyl)allyllithium, which is obtainable in virtually quantitative yield[31] from 1,3-diphenyl-2-(2-pyridyl)propene and lithium diisopropylamide, and which like 1,2,3-triphenylallyllithium[58] occurs not in the *trans,trans*- but in the *cis,trans*- and, above all in the *cis,cis*- form, does not undergo cycloaddition to activated alkenes[54].

An allyllithium compound of apparently suitable type *(58)*, with *substituents readily removable* after the cycloaddition, is *(63)*. This unstable compound, obtainable at −60 °C in THF, reacts rapidly with azobenzene at −60 °C to give the adduct *(64a)* [detected as *(64b)*], which gives rise to the cycloadduct *(65)* in a second reaction step (at 65 °C) requiring more activation energy[54, 59]. Since in this instance a two-step mechanism has been clearly established, it may be assumed that other 1,3-anionic cycloadditions also proceed in two steps. Compound *(64b)* can be converted into the pyrazolidine *(64c)* by treatment with lithium diisopropylamide in THF at 65 °C and subsequent hydrolysis.



4.3. 1,3-Diphenylpropargyllithium

Owing to its sp-hybridization, the central carbon of the 1,3-diphenylpropargyl anion of *(66)* exhibits relatively high electronegativity. Consequently, it appeared possible that this anion might also enter into 1,3-anionic cycloadditions. In fact, the cycloadduct *(67a)* is formed on reaction of lithium diisopropylamide and 1,3-diphenylpropyne, which in *n*-hexane leads initially to *(66)* (60% yield) and 1,3-diphenylallene[60]; hydrolysis of *(67a)* with water gives its protonation product *(67b)*[53] in 61% yield. The steric arrangement of the substituents in this substance has not yet been established.

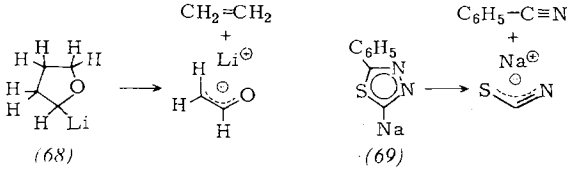


5. 1,3-Anionic Cycloeliminations and the Influence of the Metal in 1,3-Anionic Cycloadditions

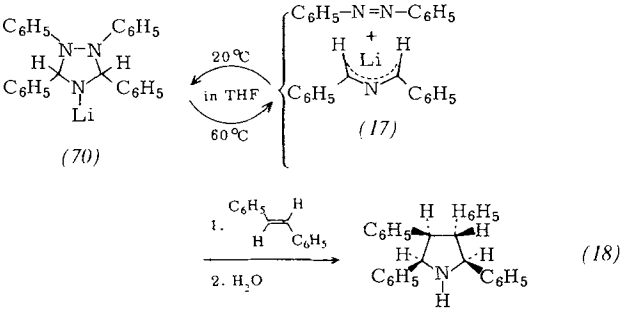
5.1. Cycloeliminations

A number of cycloeliminations corresponding to a reversal of 1,3-anionic cycloaddition are known:

The elimination of olefins from lithiated 1,3-dioxolanes[61] and 1,3-dithiolanes (see Scheme 1)[61] in a reaction of this type has found preparative application. The analogous scission of lithiated tetrahydrofuran *(68)*[62] not infrequently proves troublesome in the case of organometallic reactions. The cleavage of *(69)* into a nitrile and sodium thiocyanate[63] shows that aromatic systems can also decompose in this fashion. Whereas these and similar[64] cycloeliminations give rise to low-energy anions, which according to currently available information cannot undergo cycloaddition to unsaturated systems, we have observed analogous reactions yielding relatively high-energy anions capable of cycloaddition: The lithiated triazolidine *(70)*, obtained in 73% yield by the cycloaddition of *trans,trans*-1,3-diphenyl-2-azaallyllithium *(17)* to azobenzene in THF at 20 °C, decomposes largely into the components in the same solvent at 65 °C. 51% of azobenzene was set free on heating pure *(70)* to 60 °C in THF for 90 min; the co-product *(17)* could be trapped as the pyrrolidine derivative *(18)* (20%) with *trans*-stilbene[21,28]. This reaction opens up the third route to 2-azaallyllithium compounds (cf. Section 3.1).



An analogous cycloelimination of *(17)*, leading to isomerization, and that of 1-phenyl-1,2-diazaallyllithium *(50)*, have already been mentioned in Sections 3.2.1 and 4.1 respectively.



5.2. Influence of the Metal

In contrast to classical cycloadditions (Diels-Alder reaction, 1,3-dipolar cycloaddition), whose mechanism has been largely elucidated, a new structural element is involved in 1,3-anionic cycloaddition, *i.e.* the positively charged metal atom. Its influence on the cycloaddition and its reversal is therefore of considerable theoretical and practical interest.

We found that lithium and sodium on the one hand, and potassium and magnesium on the other, exert markedly different effects. Whereas 1,3-diphenyl-2-azaallyllithium and -sodium[65] react in THF at 20 °C with *trans*-stilbene to the extent of 80—85 and 60—65%, respectively, yielding 2,3,4,5-tetraphenylpyrrolidinelithium or -sodium, the analogous cycloaddition of 1,3-diphenyl-2-azaallylmagnesium bromide[65] was less than 5% effective, and that of the corresponding potassium compound was less than 10% effective[19,66]. The *reversal* of 1,3-anionic cycloadditions is distinctly favored in

the case of 2,3,4,5-tetraphenylpotassium compared with the corresponding lithium compound[19].

6. Outlook

Priority should be given to the development of a versatile method of synthesizing five-membered *carbocyclic* compounds in accordance with the principle of 1,3-anionic cycloaddition. Several of the reactions outlined in this paper have a direct counterpart in the field of 1,3-dipolar cycloaddition. Future applications of 1,3-anionic cycloaddition to the synthesis of five-membered *heterocycles* will therefore undoubtedly benefit from the experience accumulated for 1,3-dipolar cycloadditions. However, 1,3-anionic cycloadditions also have common features (metal and thus ligand participation, possibility of carbocyclic synthesis and catalytic synthesis, stepwise mechanism, tendency to undergo side reactions) with "transition-metal-catalyzed cyclizations"[67], which could be regarded as a sequence of concerted ring-closure reactions in which the metal constitutes a member of the ring ("metala ring closures"[67]). Approaches to this versatile type of reaction should therefore plainly be investigated through variations in the metal and in the organic components. In mechanistic studies priority should be given to the question whether the mechanism is single-step or two-step, hitherto settled only in one case.

The author wishes to express his sincere gratitude to all those participating in these investigations, and especially to Dr. Edgar Köppelmann and Dr. Rudolf Eidenschink for their individual creative efforts. Thanks are also due to the Deutsche Forschungsgemeinschaft and the Verband der Chemischen Industrie e. V. for effective financial support.

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German version: Angew. Chem. *86*, 715 (1974)
Translated by Express Translation Service, London

[1] 1,3-Anionic Cycloaddition, Part 11. – Part 10: [28].

[2] *Th. Kauffmann* and *R. Eidenschink*, Angew. Chem. *83*, 794 (1971); Angew. Chem. internat. Edit. *10*, 739 (1971).

[3] *K. Clusius* and *H. Hürzel*, Helv. Chim. Acta *37*, 798 (1954); *I. Ugi*, Advan. Heterocycl. Chem. *3*, 373 (1964); *R. Huisgen*, Angew. Chem. *72*, 359 (1960).

[4] *G. Wittig* and *E. Knauss*, Chem. Ber. *91*, 895 (1958); cf. also *C. F. Huebner* and *I. M. Donoghue*, J. Org. Chem. *33*, 1678 (1968).

[5] *W. T. Ford*, *R. Radue*, and *J. A. Walker*, Chem. Commun. *1970*, 966.

[6] The hypothetical primary steps in the reactions of α-lithium alkylisocyanides with carbonyl compounds and nitriles are analogous to these cycloadditions. See *U. Schöllkopf*, Angew. Chem. *82*, 795 (1970); Angew. Chem. internat. Edit. *9*, 763 (1970).

[7] *Th. Kauffmann*, *H. Berg*, and *E. Köppelmann*, Angew. Chem. *82*, 396 (1970); Angew. Chem. internat. Edit. *9*, 380 (1970).

[8] *R. Huisgen*, Angew. Chem. *75*, 742 (1963); Angew. Chem. internat. Edit. *2*, 633 (1963).

[9] *R. B. Woodward* and *R. Hoffmann*, Angew. Chem. *81*, 797 (1969); Angew. Chem. internat. Edit. *8*, 781 (1969).

[10] As a component part of organolithium compounds.

[11] *G. Wittig* and *H. Reiff*, Angew. Chem. *80*, 8 (1968); Angew. Chem. internat. Edit. *7*, 7 (1968).

[12] *C. R. Hauser*, *I. C. Flur*, and *S. W. Kantor*, J. Amer. Chem. Soc. *71*, 294 (1949), describe the preparation of 1,1,3-triphenyl-2-azaallylpotassium and its reaction with carbon dioxide.

[13] *Th. Kauffmann*, *E. Köppelmann*, and *H. Berg*, Angew. Chem. *82*, 138 (1970); Angew. Chem. internat. Edit. *9*, 163 (1970).

[14] *R. Eidenschink*, Dissertation, Universität Münster 1973.

[15] *H.-G. Leonhardt*, Diplomarbeit, Universität Münster 1971.

[16] *E. Köppelmann*, Dissertation, Universität Münster 1971, as well as unpublished work 1971. For further investigations on the metalation of azomethines, see [17].

[17] *E. Köppelmann*, Diplomarbeit, Universität Münster 1968.

[18] *Th. Kauffmann*, *K. Habersaat*, and *E. Köppelmann*, Angew. Chem. *84*, 262 (1972); Angew. Chem. internat. Edit. *11*, 291 (1972).

[19] *K. Habersaat*, Dissertation, Universität Münster, planned for 1974.

[20] The sodium and potassium compounds corresponding to *(13a)* underwent similar ring cleavage in THF at 30—40 °C. In contrast, no opening of the ring was observable in the case of the analogous bis-*cis*-2,3-diphenylaziridinylnickel [19].

[21] *A. Busch*, Dissertation, Universität Münster, 1974.

[22] *H. Berg* and *Th. Kauffmann*, experiments conducted in 1970.

[23] *B. Bannert* and *Th. Kauffmann*, experiments conducted in 1973.

[24] A solution of 1,3-diphenyl-2-azaallyllithium (irrespectively of whether it had been obtained by ring opening from *N*-lithio-*cis*-2,3-diphenylaziridine at 40—60 °C or by the action of 1 mol of lithium diisopropylamide on *N*-benzylidenebenzylamine at −60 °C) adjusted to 0 °C, and left to stand for 1 h, contained at the end of this period exclusively the *trans,trans* compound *(17)*, although the *cis,trans* form *(15)* [25] was also formed alongside the *trans,trans* form when the second preparation method was used. 1,3-Diphenylallyllithium has also been found to be present exclusively in the *trans,trans* configuration in THF at 0 °C: *H. H. Freedmann*, *V. R. Sandel*, and *B. P. Thill*, J. Amer. Chem. Soc. *89*, 1762 (1967).

[25] *Th. Kauffmann* and *E. Köppelmann*, Angew. Chem. *84*, 261 (1972); Angew. Chem. internat. Edit. *11*, 290 (1972).

[26] *A. Eckel*, *R. Huisgen*, *R. Sustmann*, *G. Wallbillich*, *D. Grashey*, and *E. Spindler*, Chem. Ber. *100*, 2192 (1967).

[27] *J. H. Hall* and *R. Huisgen*, Chem. Commun. *1971*, 1187.

[28] *Th. Kauffmann*, *A. Busch*, *K. Habersaat*, and *B. Scheerer*, Tetrahedron Lett. *1973*, 4047.

[29] *R. Eidenschink*, Diplomarbeit, Universität Münster 1971.

[30] *Th. Kauffmann*, *H. Berg*, *E. Ludorff*, and *A. Woltermann*, Angew. Chem. *82*, 986 (1970); Angew. Chem. internat. Edit. *9*, 960 (1970).

[31] *A. Woltermann* and *Th. Kauffmann*, unpublished work 1970—1973.

[32] The open-chain structure follows primarily from the CN double bond band in the IR at *ca.* 1640 cm^{-1}, as well as from the findings that the molecular mass line in the mass spectrum of the products is weaker and the products are less resistant to dilute hydrochloric acid than in the case of the cyclic compounds. The ^{1}H-NMR spectra are not informative [21].

[33] *E. Ludorff* and *Th. Kauffmann*, unpublished work 1970.

[34] Nucleophilic aminomethylations are also possible with the reagents $N{\equiv}C^{\ominus}$, $O_2N-CH_2^{\ominus}$, and $C{=}N-CH_2^{\ominus}$ (cf. [6]).

[35] *Th. Cuvigny* and *P. Hullot*, C. R. Acad. Sci. *C 272*, 862 (1971).

[36] *U. Tannert*, Dissertation, Universität Münster 1973. Like the methanolate residue in the hypothetical compounds *(33)*, the lithium in 2-azaallyllithium compounds could in theory be attached to the nitrogen. This is unlikely in view of the spontaneous rearrangement *(15)* → *(17)*. If the lithium in *(15)* and *(17)* were attached to the nitrogen, the *cis,trans* form *(15)* would be more favorable than the *trans,trans* form *(17)* [21], due to group congestion.

[37] *A. Busch*, Diplomarbeit, Universität Münster 1971.

[38] *Th. Kauffmann* and *R. Eidenschink*, Angew. Chem. *85*, 583 (1973); Angew. Chem. internat. Edit. *12*, 568 (1973).

[39] The structure of this compound (which still has not been obtained in pure form) was checked by decomposition to α-aminophenylacetic acid [41].

[40] A corresponding regioselectivity was observed in the case of 1,3-dipolar cycloadditions to isocyanates and isothiocyanates. On the other hand, the 1,3-dipolar diphenylnitrilimine undergoes cycloaddition in approximately equal measure to the CN and CS double bonds of phenyl isothiocyanate [8].

[41] *U. Brandl* and *Th. Kauffmann*, experiments performed in 1973.

[42] *Th. Kauffmann*, *A. Busch*, *K. Habersaat*, and *E. Köppelmann*, Angew. Chem. *85*, 584 (1973); Angew. Chem. internat. Edit. *12*, 569 (1973).

[43] *B. Scheerer*, Dissertation, Universität Münster, planned for 1974.

[44] Dehydrobenzene cannot be produced in ether or THF from chlorobenzene and diphenyl-2-azaallyllithium compounds.

[45] *K. Habersaat*, Diplomarbeit, Universität Münster 1971.

[46] Studies have shown that *trans,trans*-1,3-diphenyl-2-azaallyllithium *(17)* undergoes cycloaddition to *N*-benzylideneaniline approximately 2.1 times as fast as to *trans*-stilbene [21].

[47] Review: *R. J. Cotter* and *M. Matzner*: Ring-Forming Polymerisations (3 volumes). Academic Press, New York 1969 and 1972.

[48] *D. Berger*, Dissertation, Universität Münster 1970.

[49] *Th. Kauffmann*, *D. Berger*, *B. Scheerer*, and *A. Woltermann*, Angew. Chem. *82*, 987 (1970); Angew. Chem. internat. Edit. *9*, 961 (1970).

[50] *B. Scheerer*, Diplomarbeit, Universität Münster 1970.

[51] *Th. Kauffmann*, Angew. Chem. *76*, 206 (1964); Angew. Chem. internat. Edit. *3*, 342 (1964).

[52] Cf. *M. J. S. Dewar*, Angew. Chem. *83*, 859 (1971); Angew. Chem. internat. Edit. *10*, 761 (1971).

[53] *R. Eidenschink* and *Th. Kauffmann*, Angew. Chem. *84*, 292 (1972); Angew. Chem. internat. Edit. *11*, 292 (1972).

[54] *W. Bannwarth*, Diplomarbeit, Universität Münster 1974; *W. Bannwarth, R. Eidenschink*, and *Th. Kauffmann*, Angew. Chem. *86*, 476 (1974); Angew. Chem. internat. Edit. *13*, 468 (1974).

[55] A cycloaddition of this type might take place in the formation of a cyclic dimer (39%) during the action of sodium on α-methylstyrene (*M. Kolobielski* and *H. Pines*, J. Amer. Chem. Soc. *79*, 5820 (1957)).

[56] *G. Boche* and *D. Martens*, Angew. Chem. *84*, 768 (1972); Angew. Chem. internat. Edit. *11*, 724 (1972).

[57] *G. Boche*, personal communication 1973.

[58] *J. E. Mulvaney* and *D. Savage*, J. Org. Chem. *36*, 2592 (1971).

[59] The reactions of *(63)* and similar compounds with alkenes and other unsaturated compounds are now in the course of thorough investigation; cf. ref. [54].

[60] Rearrangement of 1,3-diphenylpropyne to 1,3-diphenylallene by bases: *E. V. Dehmlow*, Chem. Ber. *100*, 3260 (1967); *H. A. Staab* and *H.-A. Kurmeier*, *ibid. 101*, 2697 (1968).

[61] *D. Seebach*, Angew. Chem. *81*, 690 (1969); Angew. Chem. internat. Edit. *8*, 639 (1969), and literature cited therein; mechanism: *K. D. Berlin, B. S. Rathore* and *M. Peterson*, J. Org. Chem. *30*, 226 (1965).

[62] *R. B. Bates, L. M. Kroposki*, and *D. E. Potter*, J. Org. Chem. *37*, 560 (1972).

[63] *A. Alemagna, T. Baccetti*, and *C. Rizzi*, Gazz. Chim. Ital. *102*, 311 (1972).

[64] *L. Claisen*, Ber. Deut. Chem. Ges. *36*, 3673 (1903); *J. Goerdeler, J. Ohm*, and *O. Tegtmeyer*, Chem. Ber. *89*, 1534 (1956); *R. L. Letsinger* and *D. F. Pollart*, J. Amer. Chem. Soc. *78*, 6079 (1956); *H. Kloosterziel, J. A. A. van Drunen*, and *P. Galama*, Chem. Commun. *1969*, 885; *P. Eberhard* and *R. Huisgen*, J. Amer. Chem. Soc. *94*, 1345 (1972).

[65] 1,3-Diphenyl-2-azaallylsodium and -potassium were prepared in solution by the thermal ring opening of *cis*-1,2-diphenyl-1-aziridinylsodium and -potassium in THF at 20°C [19], as well as by the action of $NaNH_2$ or KNH_2 on *N*-benzylidenebenzylamine in ether at 0°C [17, 66]. A solution of 1,3-diphenyl-2-azaallylmagnesium bromide was obtained by the action of mesitylmagnesium bromide on *N*-benzylidenebenzylamine in THF at 67°C [66].

[66] *D. Berger* and *Th. Kauffmann*, unpublished work.

[67] Cf. *P. Heimbach* and *R. Traunmüller*: Chemie der Metall-Olefin-Komplexe. Verlag Chemie, Weinheim 1970; *W. P. Giering* and *M. Rosenblum*, J. Amer. Chem. Soc. *93*, 5299 (1971); *A. Rosau, M. Rosenblum*, and *J. Tancrede*, *ibid. 95*, 3062 (1973).

Dinitrogen-Transition Metal Complexes: Synthesis, Properties, and Significance

By Dieter Sellmann[*]

Compared to the large number of CO complexes, N_2 complexes are still rare. In certain cases they may be formed from N_2 gas and metal compounds under physiological conditions, and are therefore frequently considered as possible intermediates in N_2 assimilation. However, despite numerous attempts it has not yet been possible to reduce the N_2 ligand of a fully characterized N_2 complex to NH_3. This negative evidence recently prompted the discoverers of the first dinitrogen complex, the $[Ru(NH_3)_5N_2]^{2\oplus}$ ion isolated in 1965, to express doubt whether such complexes really do play a part in the enzymatic reduction of N_2. The latest findings nevertheless incline toward a somewhat more optimistic view. Thus, the mild partial reduction of the N_2 ligand in metal complexes with inert gas configuration, hitherto considered nonreducible, justifies the hope that a suitable system permitting the catalytic reduction of molecular nitrogen under normal conditions will one day be found. Even apart from any technical potential, the N_2 complexes constitute an interesting chapter of modern inorganic chemistry.

1. Introduction

Under normal conditions molecular nitrogen is usually found to be chemically inert. Thus, reactions involving the N_2 molecule generally require drastic conditions, *e. g.* elevated temperatures and pressures, as in the Haber-Bosch process.

However, nature is capable of converting atmospheric nitrogen enzymatically during N_2 assimilation into ammonia and amino acids under mild physiological conditions (15°C, 0.8 atm. N_2, aqueous medium). In chemistry, only one defined reaction of the N_2 molecule is currently known which also proceeds under physiological conditions: the reaction with metal compounds to yield dinitrogen complexes. This reaction can clearly be considered as a model for the absorption of atmospheric nitrogen by the N_2-assimilating enzymes in nature. Hence the fundamental significance of the reaction and its products.

What features characterize the reaction partner, which allows reduction of the normally inert molecular nitrogen during the course of assimilation?

Biochemists are trying to answer this question by the isolation and study of the nitrogen-assimilating enzymes, the nitrogenases; purely chemical means are employed by chemists attempting to simulate nature *in vitro* by fixing molecular nitrogen to synthetic compounds. Since transition metals—especially molybdenum and iron—are present in the nitrogenases, systems containing these metals are of particular interest. What the chemist wants is a defined system in which he can follow the reduction of the N_2 molecule step by step.

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Isolable and unambiguously characterizable model substances thus appear especially important.

N_2-fixing chemical systems can be roughly divided into protic and aprotic. The impetus which led to the investigation of the aprotic group was the observation that Ziegler-Natta catalysts and similar compounds absorb nitrogen and reduce it to nitride-type products. The fundamental difference between these systems and the nitrogenases lies in their aprotic character: the hydrolytic susceptibility of the organometallic components (*e. g.* Grignard reagents, alkylaluminum derivatives, alkali metal naphthalides) makes rigorous exclusion of water essential. The reactions which proceed in such systems are therefore reminiscent of the well-known reaction between nitrogen and lithium to give Li_3N. Coupled with the fact that, with few exceptions, unambiguously characterized compounds could not be isolated, this proved to be a disadvantage compared with the second group, the protic systems. These are capable of existing in aqueous or other proton-containing solvents, and the reaction with molecular nitrogen yields well-defined products, the N_2 complexes, which will be discussed below[1].

2. Definition, Nomenclature, Possible Modes of Bonding

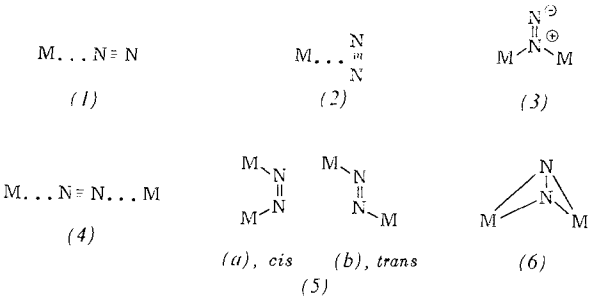
Dinitrogen complexes are coordination compounds which contain the N_2 molecule as ligand. The first example of this class of compounds was discovered by *Allen* and *Senoff* in 1965[2]. The attempted synthesis of ammine complexes from $RuCl_3$ and hydrazine hydrate did not yield the expected $[Ru(NH_3)_6]^{2\oplus}$ ion but the stable complex $[(NH_3)_5RuN_2]Cl_2$ instead.

Long before this discovery, the realization that N_2-assimilating bacteria require molybdenum in order to fix atmospheric nitrogen had led to the hypothesis that dinitrogen-transition metal complexes play a part in this process[3]. However, numerous unsuccessful attempts to prepare such complexes as well as subsequent theoretical considerations led to the assumption that these compounds were not stable.

The isolation of the first stable N_2 complex, and the hope of obtaining information on N_2 assimilation through the study of this new class of compounds, stimulated an intensive search for further examples. The result is a respectable number of new dinitrogen complexes; compared with the hundreds of complexes formed by the isoelectronic carbon monoxide, however, they must still be considered a rarity.

According to the IUPAC rules[4a], the N_2 molecule is named "dinitrogen" when it is a formally uncharged ligand in coordination compounds. Other proposals such as "nitrogenyl" (by analogy with "carbonyl"), "nitrogeno", or "nitrogen" should therefore be avoided.

In principle, several possibilities are conceivable for the linkage between dinitrogen and metals (Scheme 1). These are in particular: terminal ("end-on") bonding [*(1)*], lateral ("side-on", or "edge-on") bonding [*(2)*], bridge bonding *via* one of the N atoms [*(3)*], terminal bridge bonding *via* both N atoms with a metal atom on each nitrogen [*(4)*, *(5)*] or two metal atoms on each nitrogen [*(6)*]. *(1)* and *(3)* correspond to the bonding in terminal and bridged carbonyl complexes respectively, *(2)* is comparable to the bonding in acetylene complexes. In *(1)*, *(2)*, and *(4)* the triple bond in the N_2 molecule is largely retained, but not so in *(3)*, *(5)*, and *(6)*. *(5)* is therefore to be regarded as a complex of the doubly deprotonated diimine HN=NH, and *(6)* as a fully deprotonated hydrazido complex, rather than as dinitrogen complexes.



Scheme 1. Linkage possibilities of the N_2 ligand.

So far, only bonds of types *(1)*, *(4)*, and *(6)* have been unequivocally demonstrated in N_2 complexes; *(2)* has been postulated. The structural unit *(6)* is present in the complex $[\{(PhLi)_3Ni\}_2N_2 \cdot 2Et_2O]_2$[*]. Here the two Ni atoms and the two atoms of the N_2 molecule occupy the corners of a distorted tetrahedron; two such $[Ni_2N_2]$ units are bridged *via* two Li atoms. A side-on π bond between the N_2 molecule and the metal centers is considered as a possibility; accordingly, ethylene readily displaces the N_2 ligand from the complex. The length of the N—N bond was found by X-ray structure analysis to be 1.35 Å, the highest value yet encountered in a N_2 complex. This value approaches that of an N—N single bond (1.47 Å) and points to a considerable activation of the N_2 molecule[4b].

A Pt complex, formed from *cis*-$[PtCl_2(PPh_3)_2]$ and hydrazine, contains the structural unit *(3)* in protonated form[5] (Fig. 1).

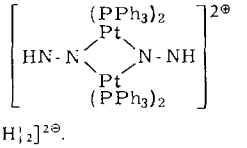


Figure 1. Schematic structure of $[\{Pt(PPh_3)_2N_2H\}_2]^{2\oplus}$.

Molecules related to terminal N_2 complexes include N_2O, HN_3, CH_2N_2, $C_6H_5N_2^{\oplus}X^{\ominus}$, and 1,10-$B_{10}H_8(N_2)_2$, which may be considered as an internal diazonium salt[6]. These nonmetallic compounds containing the N_2 grouping are not discussed here, nor are substances such as azobenzene, Ph—N=N—Ph, which are only formally related to bridged N_2 complexes.

3. Preparation of Nitrogen Complexes

Table 1 summarizes the data on unequivocally characterized N_2 complexes. Apart from chloride and ammonia, phosphanes and hydride ions appear remarkably often as coligands of N_2. It was not until very recently that N_2 complexes were synthesized with arene and CO ligands. In view of the high sulfur content of the nitrogenases, it is surprising that so far only one very unstable and poorly characterized N_2

[*] For abbreviations see Table 1, footnote [a].

Table 1. Some dinitrogen complexes.

Complex [a]	Color	Electron configuration	$\nu_{N\equiv N}$ [cm^{-1}]	Ref.
$[C_6H_6Cr(CO)_2N_2]$	red	d^6	2145 [b]	[10]
$[(mes)Cr(CO)_2N_2]$	reddish-brown	d^6	2132 [b]	[11]
$[(hmb)Cr(CO)_2N_2]$	reddish-brown	d^6	2112 [b]	[11]
trans-$[Mo(N_2)_2(diphos)_2]$	yellow-orange	d^6	2040 [c] 1975	[12, 13]
$[(tol)Mo(PPh_3)_2N_2]$	orange	d^6	2000 [c]	[14]
trans-$[Mo(N_2)_2(PMe_2Ph)_2(dpse)]$	dark red	d^6	1925 [c]	[13]
cis-$[W(N_2)_2(PMe_2Ph)_4]$	yellow	d^6	1931 [d] 1998	[15]
trans-$[W(N_2)_2(diphos)_2]$	orange	d^6	1953 [d]	[15]
$[C_5H_5Mn(CO)_2N_2]$	reddish-brown	d^6	2169 [b]	[16]
$[C_5H_5Re(CO)_2N_2]$	yellow	d^6	2141 [b]	[17]
trans-$[ReCl(N_2)(PMe_2Ph)_4]$	yellow	d^6	1925 [e]	[18]
trans-$[ReCl(N_2)(diphos)_2]$	yellow	d^6	1980 [c]	[18]
$[ReCl(N_2)(CO)_2(PPh_3)_2]$	yellow	d^6	2060 [d]	[19]
trans-$[ReCl(N_2)(diphos)_2]^{\oplus}$	red	d^5	2060	[20a, 20b]
$[FeH_2(N_2)(PEtPh_2)_2]$		d^6	1989 [g]	[21]
$[FeH_2(N_2)(PEtPh_2)_3]$	yellow	d^6	2057 [g]	[21]
trans-$[FeH(N_2)(depe)_2]^{\oplus}$	orange	d^6	2090	[22]
$[RuH_2(N_2)(PPh_3)_3]$	white	d^6	2147 [g]	[23]
$[RuCl(N_2)(das)_2]^{\oplus}$	white	d^6	2130	[24]
$[Ru(NH_3)_5N_2]Br_2$	yellowish	d^6	2114 [g]	[25]
cis-$[Ru(en)_2(H_2O)N_2]^{2\oplus}$	yellowish	d^6	2130 [g]	[26]
cis-$[Ru(en)_2(N_2)_2]^{2\oplus}$	yellowish	d^6	2220 [g] 2190	[26]
$[RuCl_2(N_2)(H_2O)_2THF]$	white	d^6	2153 [g]	[27]
$[OsH_2(N_2)(PEtPh_2)_3]$		d^6	2085 [g]	[28]
mer-$[OsCl_2(N_2)(PMe_2Ph)_3]$	white	d^6	2082 [d]	[29]
mer-$[OsHCl(N_2)(PMe_2Ph)_3]$	white	d^6	2057 [d]	[30]
$[Os(NH_3)_5N_2]Br_2$ [i]	yellowish	d^6	2028 [g]	[31]
cis-$[Os(NH_3)_4(N_2)]_2Cl_2$		d^6	2120 2175	[32]
$[CoN_2(PPh_3)_3]$	red	d^9	2093 [f]	[33]
$[CoH(N_2)(PPh_3)_3]$	red-orange	d^8	2090 [d]	[34]
$Na[CoN_2(PEt_2Ph)_3]$	black	d^{10}	1875 [f]	[35]
$[RhCl(N_2)(PPh_3)_2]$	yellowish	d^8	2152 [g]	[36]
$[IrCl(N_2)(PPh_3)_2]$	yellow	d^8	2105 [c]	[37]
$[NiH(N_2)(PEt_3)_2]$	orange	d^9	2076 [d]	[38]
$[\{(C_5H_5)_2Ti\}_2N_2]$	blue	d^3, d^3	1280	[39]
$[\{(mes)Cr(CO)_2\}_2N_2]$	red	d^6, d^6		[11]
$[\{(hmb)Cr(CO)_2\}_2N_2]$	red	d^6, d^6		[11]
$[\{(C_6H_6)(PPh_3)_2Mo\}_2N_2]$	brown	d^6, d^6	1910 [h]	[14]
$[(tol)(PPh_3)_2Mo-N_2-Fe(C_5H_5)(dmpe)]^{\oplus}$	brown	d^6, d^6	1930	[14]
trans-$[(PMe_2Ph)_4ClRe-N_2-CrCl_3(THF)_2]$	dark red	d^6, d^3	1875	[40]
$[\{C_5H_5Fe(dmpe)\}_2N_2]^{2\oplus}$	yellowish	d^6, d^6	2054 [h]	[41]
$[ReCl(PMe_2Ph)_4\ N_2\cdots MoCl_4(OMe)]$	red-black	d^6, d^1	1660	[67b]
$[(PPh_3)_2FeH(OEt_2)\cdots N_2-Fe(OEt_2)(PPh_3)_2]$	red	d^8, d^8	1761	[42]
$[\{(NH_3)_5Ru\}_2N_2]^{4\oplus}$	gold yellow	d^6, d^6	2100 [h]	[43]
$[\{(H_2O)_5Ru\}_2N_2]^{4\oplus}$	gold brown	d^6, d^6	2080	[44]
$[(NH_3)_5Ru\cdots N_2\cdots Os(NH_3)_5]^{4\oplus}$		d^6, d^6		[45]
$[N_2(NH_3)_4Os-N_2-Os(NH_3)_5]^{5\oplus}$		d^6, d^5		[46]
$[\{(PEt_2Ph)_3Co\}_2N_2]$	dark brown	d^9, d^9		[35]
$[\{(PCy_3)_2Ni\}_2N_2]$	dark red	d^{10}, d^{10}		[47]
$[\{(PhLi)_3Ni\}_2N_2\cdot 2Et_2O]_2$	dark red	d^{10}, d^{10}		[4b]

[a] Abbreviations: acac = 3,5-pentanedionate; Cy = cyclohexyl; das = ethylenebis(diphenylarsane) $Ph_2AsCH_2CH_2AsPh_2$; depe = ethylenebis(diethylphosphane) $Et_2PCH_2CH_2PEt_2$; diphos = ethylenebis(diphenylphosphane) $Ph_2PCH_2CH_2PPh_2$; dmpe = ethylenebis(dimethylphosphane) $Me_2PCH_2CH_2PMe_2$; dpse = 1,2-bis(phenylthio)ethane $PhSCH_2CH_2SPh$; en = ethylenediamine; Et = ethyl; hmb = hexamethylbenzene; M = metal; Me = methyl; mes = mesitylene; Ph = phenyl; THF = tetrahydrofuran; tol = toluene.

[b] In hexane; [c] in toluene; [d] in benzene; [e] in chloroform; [f] in tetrahydrofuran; [g] in nujol; [h] in the Raman spectrum.

[i] Recently the first N_2 complex with a porphyrin ligand was prepared; *trans*-octaethylporphinato(dinitrogen)tetrahydrofuranosmium(II); see *J. W. Buchler*, and *P. D. Smith*, Angew. Chem., in press.

complex with a sulfur-containing ligand is known: *trans*-$[Mo(N_2)_2(PMe_2Ph)_2\ (PhSCH_2CH_2SPh)]$.

Table 1 does not include N_2 complexes obtained by matrix isolation at low temperatures (*ca.* −196 °C), *e.g.* CrN_2, NiN_2, PtN_2[7], $Ni(N_2)_n$, $Pd(N_2)_m$[8], and $Ni(CO)_3N_2$[9].

Thus far three possibilities exist for the preparation of N_2 complexes:

1) Direct reaction of N_2 with a metal complex, frequently under strongly reducing conditions.

2) Conversion of a metal complex with ligands containing N—N bonds, *e.g.* N_2H_4 or $N_3^{\ominus}$.

3) Formation of an N_2 triple bond in a metal complex by reaction of ligands such as NH_3 with a nitrogen-containing reagent, *e.g.* HNO_2.

3.1. Direct Methods

A metal complex in the presence of excess ligand is reduced under N_2 by metals, metal amalgams, or hydrides.

$$[WCl_4(PMe_2Ph)_2] + Na/Hg \xrightarrow{N_2} [W(N_2)_2(PMe_2Ph)_4] \quad (1)$$

$$[MoCl_4(PMe_2Ph)_2] + Na \xrightarrow[\text{toluene}]{N_2} [Mo(N_2)_2(PMe_2Ph)_4] \quad (2)$$

$$[FeHCl(depe)_2] + NaBH_4 \xrightarrow[\text{acetone}]{N_2} [FeH(N_2)(depe)_2]BH_4 + NaCl \quad (3)$$

Alkylmetal compounds may also be used as reducing agents. Presumably they introduce an alkyl group into the metal complex; the ensuing olefin elimination produces a hydride complex which then reacts with the N_2. Suitable reactants include $AlEt_2(OEt)$, $AlEt_3$, and $Al(iBu)_3$. $AlMe_3$ yields mainly methyl complexes.

$$[Co(acac)_2] + 3\,PPh_3 + AlEt_2(OEt) \xrightarrow[\text{toluene}]{N_2} [CoN_2(PPh_3)_3] + [CoH(N_2)(PPh_3)_3] \quad (4)$$

$$[Mo(acac)_3] + 2\,\text{diphos} + Al(iBu)_3 \xrightarrow[\text{toluene}]{N_2} \textit{trans}\text{-}[Mo(N_2)_2(\text{diphos})_2] \quad (5)$$

$$[Ni(acac)_2] + PCy_3 + AlMe_3 \xrightarrow{N_2} [\{(PCy_3)_2Ni\}_2N_2] \quad (6)$$

Labile ligands in metal complexes can be displaced by N_2. These are the clearest reactions of molecular nitrogen; they proceed under mild conditions and are frequently reversible.

$$[CoH_3(PPh_3)_3] + N_2 \overset{EtOH}{\rightleftharpoons} [CoH(N_2)(PPh_3)_3] + H_2 \quad (7)$$

$$[Ru(NH_3)_5H_2O]^{2\oplus} + N_2 \overset{H_2O}{\rightleftharpoons} [Ru(NH_3)_5N_2]^{2\oplus} + H_2O \quad (8)$$

$$2[C_5H_5Fe(\text{dmpe})\text{acetone}]^{\oplus} + N_2 \xrightarrow{\text{acetone}} [\{C_5H_5Fe(\text{dmpe})\}_2N_2]^{2\oplus} + 2\,\text{acetone} \quad (9)$$

$$[(hmb)Cr(CO)_3] + THF \xrightarrow{h\nu} [(hmb)Cr(CO)_2THF] + CO \quad (10a)$$

$$2[(hmb)Cr(CO)_2THF] + N_2 \xrightarrow{THF} [\{(hmb)Cr(CO)_2\}_2N_2] + 2THF \quad (10b)$$

In some cases the intermediates cannot be isolated but immediately react further with N_2, as in the reaction according to eqs. (10a) and (10b).

3.2. Conversion of a Ligand with N—N Bonds into N_2

Most systematic syntheses of N_2 complexes were successful by this method.

$$\textit{trans}\text{-}[Ir(CO)Cl(PPh_3)_2] + PhCON_3 \xrightarrow[CHCl_3]{0\,^{\circ}C} \textit{trans}\text{-}[Ir(N_2)Cl(PPh_3)_2] + PhCONCO \quad (11)$$

$$[(PPh_3)_2Cl_2Re(O)N{=}N{-}CPh] + 2\,PPh_3 \xrightarrow{MeOH} \textit{trans}\text{-}[ReCl(N_2)(PPh_3)_4] + HCl + PhCO_2Me \quad (12)$$

$$[C_5H_5Mn(CO)_2N_2H_4] + 2H_2O_2 \xrightarrow[-40\,^{\circ}C]{Cu^{2\oplus}/THF} [C_5H_5Mn(CO)_2N_2] + 4H_2O \quad (13)$$

$$[RuCl(das)_2N_3]PF_6 + NOPF_6 \longrightarrow [RuCl(N_2)(das)_2]PF_6 + \text{by-products} \quad (14)$$

3.3. Formation of an N_2 Ligand from an N_1 Ligand

Ammine complexes can be diazotized with nitrous acid, but this method is of very limited application.

$$[Os(NH_3)_5N_2]^{2\oplus} + HNO_2 \rightarrow \textit{cis}\text{-}[Os(NH_3)_4(N_2)_2]^{2\oplus} + 2H_2O \quad (15)$$

4. Structure of Dinitrogen Complexes

4.1. Molecular Structure

That the metal-N—N or metal-N—N-metal unit in terminal N_2 complexes is approximately linear is apparent from the strong IR absorption of the N_2 stretching vibration; a side-on linkage of the N_2 ligand, as in ethylene or acetylene complexes, would produce only weak IR absorption. Clear evidence for a linear arrangement is provided by X-ray structure analysis (Fig. 2), although accurate determination of bond lengths failed in many cases owing to disorder phenomena.

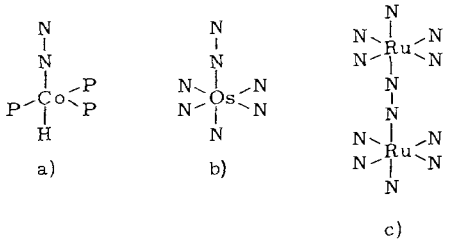


Figure 2. Schematic structures of (a) $[CoH(N_2)(PPh_3)_3]$, (b) $[Os(NH_3)_5N_2]^{2\oplus}$, and (c) $[\{Ru(NH_3)_5\}_2N_2]^{4\oplus}$.

Table 2 summarizes the most important data.

The N—N distances of coordinatively bound dinitrogen are only marginally greater than in the free N_2 molecule. The complex $[\{(PhLi)_3Ni\}_2N_2 \cdot 2Et_2O]_2$[4b], which contains the structural unit *(6)* (Scheme 1) and in which $d_{N-N} = 1.35$ Å, is an exception, as is $[ReCl(PMe_2Ph)_4{-}N_2{-}MoCl_4(OMe)]$ with $d_{N-N} = 1.21$ Å[67b]. For comparison, the length of the NN double bond (in diazomethane) is 1.24 Å and that of the NN single bond (in hydrazine) is 1.47 Å[48].

Since the nitrogenases also reduce acetylene (to ethylene), it should be pointed out that the structures of (end-on) N_2 complexes bear not the slightest resemblance to the acetylene complexes in which the two C atoms of the C_2H_2 are linked to the metal in the same manner. Instead, they are similar to acetylide complexes, *e.g.* $K_2[Cr(CO)_3(C{\equiv}CH)_3]$[56].

4.2. Bonding

The structures of N_2 complexes largely resemble those of the analogous isoelectronic CO complexes, thus revealing similarities in electronic structure. However, while carbon monoxide forms numerous mono- and poly-CO complexes, only a few monocomplexes are known for dinitrogen; among the higher complexes, only bis-N_2 species have been reported. The reason for this, and for the generally greater stability of CO complexes, lies in the electronic differences between N_2 and CO.

The following discussion of the bonding properties of N_2 and CO should throw some light on this aspect. Figure 3 shows the molecular orbital scheme of dinitrogen, as derived

Table 2. Molecular data for some dinitrogen compounds.

Compound	d_{M-N_2} [Å] [a]	d_{N-N} [Å]	$\sphericalangle_{M-N-N}$ [°]	Ref.
N_2		1.0976		[48]
$[Ru(NH_3)_5N_2Cl_2$	2.10	1.12 [b]		[49]
$[Os(NH_3)_5N_2]Cl_2$	1.84	1.12	179	[50]
$[Ru(N_3)(N_2)(en)_2]PF_6$	1.89	1.106	179.3	[51]
$[ReCl(N_2)(PMe_2Ph)_4]$	1.97	1.06 [b]	177	[52]
$[CoH(N_2)(PPh_3)_3]$	1.81	1.11	178	[53]
$[Mo(N_2)_2(diphos)_2]$	2.01	1.10	171.8	[54]
$[\{Ru(NH_3)_5\}_2N_2]^{4\oplus}$	1.928	1.124	178.3	[55]
$[\{(PCy_3)_2Ni\}_2N_2]$	1.79	1.12	178.2	[47]
$[\{(PhLi)_3Ni\}_2N_2 \cdot 2\,Et_2O]_2$		1.35		[4b]
$[ReCl(PMe_2Ph)_4—N_2—MoCl_4(OMe)]$	1.79; 1.89	1.21		[67b]
H_2CN_2	1.34	1.13	180	[48]
HNN_2	1.24	1.134	180	[48]
ON_2	1.18	1.128	180	[48]

[a] M = metal, C, N, or O.
[b] No accurate determination possible.

from UV[57] an photoelectron spectra[58], as well as from theoretical calculations[59].

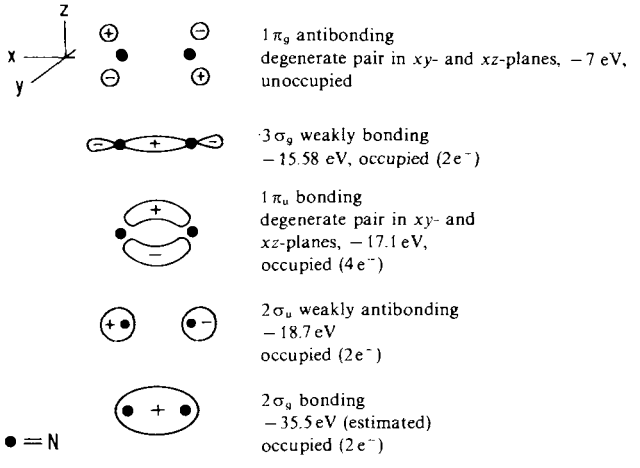


Figure 3. Molecular orbital scheme of dinitrogen.

The exceptional stability of dinitrogen compared to other diatomic molecules is a consequence of its low-lying three highest occupied bonding molecular orbitals. The actual HOMO is a bonding $3\sigma_g$ orbital of very low energy. Hence the ionization energy of N_2 is considerable (15.58 eV), approximating to that of argon (15.75 eV). The LUMO, $1\pi_g$, lies 8.6 eV above the $3\sigma_g$ orbital, *i. e.* so high that it can be occupied at best by electrons from alkali metals and other strongly electropositive metals. The absence of orbitals in the energy range between the two, *i. e.* precisely that range in which the occupied and unoccupied orbitals participating in chemical reactions are located, largely explains the low reactivity of the N_2 molecule.

While the MO scheme of carbon monoxide is very similar to that of dinitrogen, essential differences are noted in the much lower energetic stability of the highest occupied σ and of the lowest unoccupied π^* orbitals (−14.0 and −6 eV respectively) and in the smaller energy difference between these two orbitals, which is lower by 0.6 eV. In addition, the highest occupied σ orbital in CO possesses weak antibonding character; this can be deduced also from the shortening of the C—O bond from 1.128 to 1.115 Å in the ionization $CO \rightarrow CO^{\oplus}$. The ionization $N_2 \rightarrow N_2^{\oplus}$, on the other hand, results in a lengthening of the N—N bond from 1.098 to 1.117 Å[57]. Clearly the electron distribution in CO and N_2 will also differ because carbon and oxygen have different radii, electronegativities, *etc.*, whereas dinitrogen is a homonuclear molecule. CO possesses a small dipole moment ($\mu = 0.2$ D). Calculations of the electron-density distribution also show that the C atom exhibits a greater lone electron pair charge density than the O atom[60].

The metal-dinitrogen bond in N_2 complexes can be described according to the MO method by overlapping of the $3\sigma_g$ and $1\pi_g$ orbitals of the dinitrogen with suitable d orbitals of the metal (Fig. 4).

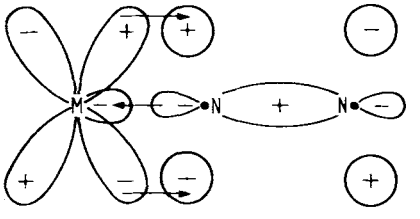


Figure 4. Scheme of the M—N_2 bond.

As in the case of the M—CO bond, a donor bond is postulated involving the $3\sigma_g$ electrons of dinitrogen and an unoccupied metal d orbital. The resulting increased electron density at the metal is reduced by back-bonding from nonbonding occupied metal d orbitals to the antibonding $1\pi_g$ orbital of the dinitrogen. The result is a synergetic σ-π double bond, *i. e.* a strengthening of the σ bonding leads to the simultaneous strengthening of the π bonding.

This type of bonding explains why N_2 complexes are less stable than CO complexes. Most metal complexes possess d orbitals (*e. g.* e_g and t_{2g} orbitals) whose energies correspond better to those of the σ and π^* orbitals of CO than to those of the N_2 molecule. This enhanced interaction increases the stability of the CO complexes.

The bond scheme illustrated in Figure 4 also explains why electronic variations result in largely analogous effects in N_2 and CO complexes.

What physical changes are to be expected in the N_2 molecule as a result of coordination if the above model of the M—N_2 bond is correct?

The N—N bond should become weaker on complex formation, since the electrons of the M—N σ bond come from a bonding orbital of the N_2 and those of the M—N π bond are transferred to an antibonding N_2 orbital. However, this conclusion has recently been disputed. According to theoretical calculations, the removal of electrons from the $3\sigma_g$ orbital should reduce the electron repulsion between the two N atoms and thereby strengthen the N_2 σ bond[61]. The weakening of the N_2 triple bond would then be mainly due to the π back-bonding.

The overall weakening of the N_2 triple bond and consequent activation of the N_2 molecule on complexing are clearly demonstrated by the marked drop in the N_2 stretching frequency, which falls by several hundred wave numbers from the value of 2331 cm^{-1} recorded for the free molecule (Raman spectrum). Furthermore, the N_2 molecule in terminal N_2 complexes is subject to strong electronic polarization, which accounts for the high intensity of the ν_{N_2} absorption in the IR spectrum. This polarization is also confirmed by the ESCA spectra of N_2 complexes. Metal-bound and terminal N atoms exhibit separate N-1s emissions, *e. g.* at 399.9 and 397.9 eV for $[ReCl(N_2)(diphos)_2]$, whereas the emission of the free N_2 molecule is observed at 411 eV. These values afford a charge difference of approximately 0.4 e between the two N atoms, the terminal one bearing the greater negative charge[62,63].

Attempts to determine the properties of the N_2-bonding coordination site in N_2 complexes have been based primarily on comparative studies, and particularly on systematic variation of the coligands of dinitrogen. However, since the stability limits of N_2 complexes are very narrow owing to the unfavorable energy of the N_2 orbitals, only a few examples are available for studying the effect of the variation of coligands on the metal-N_2 bond. Thus the reaction according to eq. (11) can only be effected with triphenylphosphane; tris(*p*-tolyl)phosphane or methyldiphenylphosphane no longer yield isolable complexes[64].

Experience has shown that the central metal of an N_2-bonding complex must exist in a low oxidation state and possess a relatively high electron density. A fitting example is $[Ru(NH_3)_5CO]^{2\oplus}$, the CO analog of $[Ru(NH_3)_5N_2]^{2\oplus}$[65]. Despite the formal double positive charge on the ruthenium, the CO compound exhibits one of the lowest ν_{CO} frequencies (1919 cm^{-1}) ever observed in terminal CO complexes.

The effect of electron density is also apparent from the series $[(benzene)Cr(CO)_2N_2]$ (ν_{N_2} = 2145 cm^{-1}), $[(mesitylene)Cr(CO)_2N_2]$ (ν_{N_2} = 2132 cm^{-1}), and $[(hexamethylbenzene)Cr(CO)_2N_2]$ (ν_{N_2} = 2112 cm^{-1}). Introduction of the "electron-donating" CH_3 substituents into the benzene ring increases the electron density at the chromium. As a result the frequency of the N_2 stretching vibration decreases; the bond scheme in Figure 4 indicates that this phenomenon should be associated with a strengthening of the M—N bond. Accordingly, the stability of the N_2 complexes increases in the above sequence[11].

N_2 and CO ligands influence the central metal in very similar fashion; thus, both exert approximately the same *trans* effect on the Ir—X bond in the complexes *trans*-$[IrX(X')(PPh_3)_2]$ (X = Cl, Br; X' = N_2, CO)[64]. The much-discussed question of the σ-donor and π-acceptor properties of N_2 and CO has not been finally resolved. Mössbauer spectra of *trans*-$[FeH(X)(depe)_2]BPh_4$ (X = N_2, CO) suggest that CO is a better σ-donor and π-acceptor ligand than N_2[22]. The same can be concluded from IR intensity measurements on analogous CO and N_2 complexes[66]. Such behavior can also be deduced from the electronic properties, *i. e.* the energy of the molecular orbitals, of the two molecules. However, for the compounds $[C_5H_5M(CO)_2N_2]$ (M = Mn, Re) and $[ArCr(CO)_2N_2]$ (Ar = benzene, mesitylene, and hexamethylbenzene) it appears from the ^{1}H-NMR and IR spectra that both the cyclic ligands and the CO groups must accommodate a greater electron density in the N_2 complexes than in the corresponding tricarbonylmetal complexes. In these compounds therefore the ratio of σ-donor to π-acceptor strength must be greater for dinitrogen than for carbon monoxide[11,16,17].

Surprisingly, almost the same N_2 stretching vibration frequency is often observed in dinuclear N_2 complexes as in the corresponding mononuclear complexes; examples include $[\{Ru(NH_3)_5\}_2N_2]^{4\oplus}$ (2100 cm^{-1}) and $[Ru(NH_3)_5N_2]^{2\oplus}$ (2130 cm^{-1}). Since the N—N triple bond of the N_2 molecule is weakened by coordination to one transition metal, bonding to two transition metals was expected to result in further weakening. This expectation is fulfilled only in some cases. An explanation for this phenomenon is provided by the bonding scheme of the M—N—N—M bond. If the σ bond component is regarded as largely constant, and the changes in M—N and N—N bonds are attributed mainly to variations in the π system, the scheme shown in Figure 5 applies to the π bonds of complexes with approximate fourfold symmetry, such as the complex $[\{Ru(NH_3)_5\}_2N_2]^{4\oplus}$ or the complex $[(PMe_2Ph)_4ClRe—N_2—CrCl_3(THF)_2]$[55,67a].

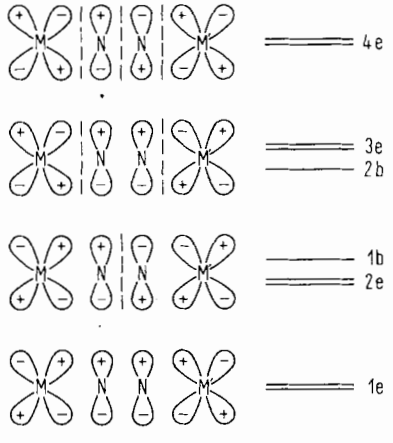


Figure 5. Qualitative molecular orbital scheme for dinuclear N_2 complexes with approximate fourfold symmetry.

The four-center molecular orbitals indicated in Figure 5 are obtained by linear combination of Md_{xz}, Np_x, and $M'd_{xz}$ orbitals. The *z*-axis is determined by the σ bond. A set of energy levels, whose energies increase with increasing nodal number of the molecular orbitals, corresponds to the molecular orbitals. Since, in addition to the orbitals shown, there exists an equivalent set of π molecular orbitals, formed from the Md_{yz}, Np_y, and $M'd_{yz}$ orbitals, the energy levels are degenerate. For the sake of simplicity they are designated as 1e, 2e, *etc.* The δ bonds formed from the Md_{xy} orbitals contribute

practically nothing to the bonding; they correspond to the 1b and 2b levels. For energetic reasons the 1e and 4e levels correspond largely to the bonding and antibonding π molecular orbitals $1\pi_u$ and $1\pi_g$, respectively, of the N_2 molecule in Figure 3. The 2e and 3e levels possess mainly metal character, as do the 1b and 2b levels.

The strengths of the M—N—N—M and of the N—N bonds thus depend chiefly on the occupancy of the e levels. Four electrons of the two N atoms fill the 1e level. This possesses bonding character for the N atoms; owing to its partial metal character, however, a weaker N—N bond results than in the free N_2 molecule. The progressive occupation of higher levels with the 12d electrons of the two $Ru^{2\oplus}$ centers (M = M') leads to a marked weakening of the N—N bond in the 2e level, as the orbitals are antibonding with respect to the N—N bond. The filling of the 1b and 2b levels leaves the N—N bond unaffected, while the occupancy of the 3e level strengthens the N—N bond since the orbitals are bonding with respect to the N atoms. Altogether there are thus five bonding filled orbitals—the bonding character of the filled M—N—N—M σ orbital must of course also be taken into account here—as against two antibonding filled orbitals with respect to the N—N bond: there is therefore hardly any difference between the N_2 bonding in $[\{Ru(NH_3)_5\}_2N_2]^{4\oplus}$ and that in $[Ru(NH_3)_5N_2]^{2\oplus}$. However, if the metal atoms do not possess sufficient electrons to fill the 2b and especially the 3e levels, a much reduced ν_{N_2} frequency is observed compared to the mononuclear complex $[ReCl(N_2)(PMe_2Ph)_4]$ ($\nu_{N_2} = 1925\ cm^{-1}$); examples include $[ReCl(PMe_2Ph)_4—N_2—CrCl_3(THF)_2]$ ($\nu_{N_2} = 1875\ cm^{-1}$), in which the Re^{I} and Cr^{III} centers can contribute a maximum of nine electrons, and $[ReCl(PMe_2Ph)—N_2—TaCl_5]$ ($\nu_{N_2} = 1695$), in which the metal atoms can contribute only six electrons for occupation of the levels.

This effect is particularly well illustrated in $[ReCl(PMe_2Ph)_4—N_2—MoCl_4(OMe)]$. This complex, containing one more electron, exhibits a ν_{N_2} frequency of $1660\ cm^{-1}$. In accordance with the low ν_{N_2} frequency, X-ray structure analysis shows the long N—N distance of 1.21 Å for the Re—N—N—Mo unit[67b].

Figure 5 also illustrates the difficulty of reducing the N_2 unit in such complexes. The electrons taken up first fill the 2b and 3e levels and thereby strengthen the N_2 bond. This is clearly no longer the case when a lowering of the fourfold symmetry resolves the degeneracy of the e levels. Such may be the case in the Fe and Ti complexes mentioned in Section 5.4.

Most of the N_2 complexes isolated so far obey the inert gas rule and are diamagnetic. Exceptions include $[CoN_2(PPh_3)_3]$ and $[\{(C_5H_5)_2Ti\}_2N_2]$, as well as adducts of Lewis acids to $[ReCl(N_2)(PMe_2Ph)_4]$.

5. Chemical Reactions of Dinitrogen Complexes

The discovery of the $[(NH_3)_5RuN_2]^{2\oplus}$ complex nurtured the hope that a pathway for definite reduction of the N_2 molecule under mild conditions had been found, a hope that was not at first fulfilled.

Attempts to reduce the complex-bound N_2 ligand usually results in its liberation. This reaction becomes easier with increasing thermal lability of the N_2 complex; the residual coordinatively unsaturated complexes can be stabilized by the addition of other ligands, *e.g.* H_2O, NH_3, pyridine, PPh_3, or solvent molecules. In the absence of such donors, the resulting complexes are frequently suitable as highly reactive catalysts for the polymerization of olefins. These N_2 complexes thus bear some resemblance to aliphatic diazo compounds which yield the reactive carbenes on loss of N_2.

5.1. Oxidation

N_2 complexes are particularly sensitive to oxidizing agents. Strong oxidizing agents are therefore frequently used for the quantitative determination of N_2[68].

$$[OsCl_2(N_2)(PEt_2Ph)_3] + {}^1/_2Cl_2 \rightarrow [OsCl_3(PEt_2Ph)_3] + N_2 \quad (16)$$

If the N_2 complexes are very stable they can sometimes be oxidized by one unit without loss of the N_2 ligand[69]:

$$[ReCl(N_2)(diphos)_2] + {}^1/_2Cl_2 \rightarrow [ReCl(N_2)(diphos)_2]Cl \quad (17)$$

The oxidized complexes are less stable than the starting compounds, in agreement with the increase of 80—100 cm^{-1} in the ν_{N_2} frequency which indicates a weakened M—N bond. Some complexes undergo reversible electrochemical oxidation, *e.g.* the $[(NH_3)_5Ru—N_2—Os(NH_3)_5]^{4\oplus}$ ion (0.1 V, rotating platinum electrode) to the ion with a fivefold positive charge[70]. Generally, however, the oxidized complexes undergo rapid secondary reactions with loss of the N_2 ligand.

5.2. Displacement or Exchange Reactions

Very stable N_2 complexes can undergo displacement reactions in which the M—N_2 unit is retained. These include the diazotization of the exceptionally stable $[Os(NH_3)_5N_2]^{2\oplus}$ ion to the $[Os(NH_3)_4(N_2)_2]^{2\oplus}$ ion[32]. (The $[Os(NH_3)_5N_2]^{2\oplus}$ ion is so stable that it resists several hours' boiling in conc. HCl.) The Re—N_2 unit in $[ReCl(N_2)(PMe_2Ph)_4]$ is also very stable and is still retained on the displacement of all the phosphane ligands[18].

$$trans\text{-}[ReCl(N_2)(PMe_2Ph)_4] + 2\,diphos \rightarrow trans\text{-}[ReCl(N_2)(diphos)_2] + 4\,PMe_2Ph \quad (18)$$

More numerous, however, are the reactions resulting in displacement of the N_2 ligand. Among them, the reversible exchange reactions of the N_2 ligand with H_2 and water [eqs. (7) and (8) respectively] are of significance for the course of N_2 assimilation. Ammonia too—the final stage of N_2 assimilation—can displace the N_2 group in dinitrogen complexes, sometimes even reversibly:

$$[CoH(N_2)(PPh_3)_3] + NH_3 \rightleftarrows [CoH(NH_3)(PPh_3)_3] + N_2 \quad (19)[70b]$$

$$[Ru(NH_3)_5N_2]^{2\oplus} + NH_3 \rightarrow [Ru(NH_3)_6]^{2\oplus} + N_2 \quad (20)$$

The exchange reactions of the Ru system have been very thoroughly studied, especially by thermochemical methods. The heat of reaction $\Delta H \mp -18.3 \pm 0.9$ kcal/mol found for eq. (8) clearly indicates the strong tendency to form the $[Ru(NH_3)_5N_2]^{2\oplus}$ ion. The greater stability of the analogous CO compound is again evident from the heat of reaction[73]:

$$[Ru(NH_3)_5H_2O]^{2\oplus} + CO \rightarrow [Ru(NH_3)_5CO]^{2\oplus} + H_2O \quad (21)$$
$$\Delta H = -36.1 \pm 1.6 \text{ kcal/mol}$$

Furthermore, the N_2 ligand in $[Ru(NH_3)_5N_2]^{2\oplus}$ can rotate in the complex, the metal-bound and the terminal N atoms interchanging places. This is deduced from the isomerization of $[(NH_3)_5Ru-{}^{14}N\equiv{}^{15}N]^{2\oplus}$ to $[(NH_3)_5Ru-{}^{15}N\equiv{}^{14}N]^{2\oplus}$, which proceeds at 25 °C in aqueous solution with a half-life of *ca.* 2 h and is approximately 45 times faster than the exchange reaction with H_2O according to eq. (8). Thus isomerization proceeds without dissociation of the N_2 ligand; the *dihapto* structure *(2)* of the M—N_2 group in Scheme 1 is postulated as a transition state[71]. However, recent studies of the Ru—N vibrations[72a] cast doubt upon this hypothesis, since the basic assignment of the ν_{Ru-N} vibration to the Ru—N_2 unit could be wrong. *Monohapto-dihapto* bonding isomerism for the N_2 ligand was recently demonstrated by ^{15}N-NMR and IR spectroscopy in $[(C_5Me_5)_2TiN_2]$ at −61 °C[72b].

5.3. Lewis Base Reactions

As explained in Section 4.2, the terminal N atom in the M—N—N unit is probably negatively polarized. Mononuclear N_2 complexes can therefore react as Lewis bases. This leads to symmetrical N_2 complexes

$$[(NH_3)_5RuN_2]^{2\oplus} + [(NH_3)_5Ru(H_2O)]^{2\oplus} \rightarrow [(NH_3)_5Ru-N_2-Ru(NH_3)_5]^{4\oplus} + H_2O \quad (22)$$
$$\Delta H = -6.7 \text{ kcal/mol}$$

as well as asymmetric N_2 complexes:

$$[(NH_3)_5RuN_2]^{2\oplus} + [(NH_3)_5Os(H_2O)]^{2\oplus} \rightarrow [(NH_3)_5Ru-N_2-Os(NH_3)_5]^{4\oplus} + H_2O \quad (23)$$

$$[(PMe_2Ph)_4ClReN_2] + [CrCl_3(THF)_3] \rightarrow [(PMe_2Ph)_4ClRe-N_2\cdots CrCl_3(THF)_2] + THF \quad (24)$$

According to eq. (24) a series of asymmetric N_2 complexes can be prepared in which the $CrCl_3(THF)_2$ grouping is replaced by $TiCl_3(THF)_2$, PF_5, $AlEt_3$, $TaCl_5$, $NbCl_5$, and many other Lewis acids[40].

In principle, the same reactions are observed for N_2-bridged complexes as for terminal N_2 complexes. As a further reaction type dissociation can yield terminal N_2 complexes, *e. g.* according to eq. (25):

$$[(PCy_3)_2Ni-N_2-Ni(PCy_3)_2] \rightleftharpoons [(PCy_3)_2NiN_2] + [Ni(PCy_3)_2] \quad (25)$$

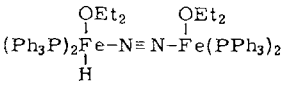
5.4. Reduction

As mentioned at the beginning of Section 5, most attempted reductions of N_2 complexes result in a loss of the N_2 unit. However, this is not always the case: $[CoN_2(PEt_2Ph)_3]$, for instance, can be reduced to an anionic N_2 complex:

$$[CoN_2(PEt_2Ph)_3] + Na/Hg \rightarrow Na[N_2Co(PEt_2Ph)_3] \quad (26)$$

Neither loss nor reduction of the N_2 ligand occur in this reaction.

Greater interest attaches to the reactions of some complexes isolated as solids from nonaqueous systems of the Ziegler-Natta type. Although they have not yet been definitely characterized, they certainly contain an N—N unit. Solvolysis of these complexes results in evolution of N_2 and in partial reduction of the N_2 ligand to hydrazine and ammonia. Thus a red complex isolated from the $(PPh_3)_2FeCl_3$/iso-C_3H_7MgCl/N_2/ether system has been postulated to have the structure:



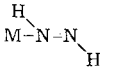
(If this structure is correct then the complex does not possess fourfold symmetry, in contrast to the Ru and Re complexes discussed in Section 4.2.) Solvolysis of this complex with HCl/ether at −50 °C yields 10% of hydrazine alongside decomposition products and N_2[42].

A deep blue complex of formula $[\{(C_5H_5)_2Ti\}_2N_2]$, for which structure *(5a)* in Scheme 1 is postulated, can be isolated from the $(C_5H_5)_2TiCl/CH_3MgI/N_2$ system. Solvolysis of this complex with methanolic HCl yields mainly dinitrogen; however, hydrazine and ammonia also appear as minor products[39a].

While these experiments show that it is possible in principle to reduce complexed dinitrogen, they have the disadvantage that with the compounds mentioned it is not possible to convert a definite N_2 complex into a definite N_xH_y complex ($x = 1$ or 2, $y = 1$, 2, 3, or 4). This was first accomplished by the reaction of well-defined bis-(dinitrogen) complexes of molybdenum and tungsten with concentrated HCl[74]:

$$[M(N_2)_2(diphos)_2] \xrightarrow{+HCl} [MCl_2(N_2H_2)(diphos)_2] + N_2 \quad (27)$$

One N_2 ligand is eliminated, the central metal is oxidized, and the other N_2 ligand is reduced to an N_2H_2 moiety. The authors favor a diimine complex of the type



for the M—N_2H_2 group. However, IR and ^{1}H-NMR spectroscopic data do not rule out a metal hydrazido structure M=N—NH_2[82].

The formation of N—C bonds in the reaction of N_2 complexes with *e. g.* acyl chlorides had been observed previously[20b-20d].

A metal-hydrazido structure has been confirmed for $[W(N_2H_2)Cl(diphos)_2]BPh_4$ by X-ray structure analysis. The observed relatively short N—N distance of 1.37 Å suggests partial double bond character of the M—N—N bond as in $[W\cdots N\cdots NH_2]^{\oplus}$[83].

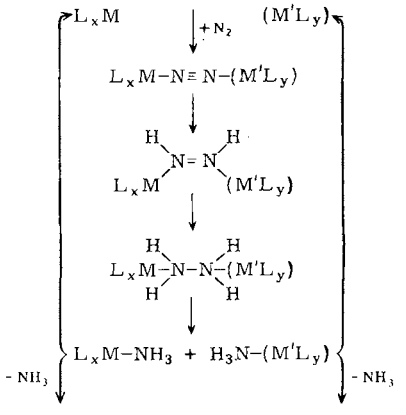
6. Dinitrogen Complexes and Other Potential Intermediates of N_2 Assimilation

Coordination of dinitrogen to a metal was suspected to be the decisive step in N_2 assimilation long before the isolation of active nitrogenase extracts from natural sources and the synthesis of stable N_2 complexes. Biochemical studies have contributed greatly to our understanding of N_2 assimilation, but it has not been possible to isolate any intermediates. Even today, all we know for certain is that the process

starts with atmospheric nitrogen and yields ammonia. Recent years have seen the synthesis of model substances which enable the chemist to develop precise and experimentally verifiable concepts concerning the reduction of dinitrogen to ammonia.

It is unlikely that the N_2 molecule takes up six electrons and six protons and decomposes to ammonia in a single step; a stepwise reduction is much more probable. Study of the intermediates therefore acquires considerable significance because such information is indispensable for the simulation of N_2 assimilation *in vitro* and for the development of technical catalysts for reduction of gaseous dinitrogen, *e.g.* to hydrazine under normal conditions.

A series of mechanisms has been proposed in recent years for the reduction of dinitrogen with nitrogenases[75]. In accordance with biochemical data, the most likely alternatives postulate two-electron reduction steps and unaminously assume that the dinitrogen is reduced to ammonia *via* diimine and hydrazine (Scheme 2).



Scheme 2. Intermediates of N_2 reduction, greatly simplified.

According to this scheme, the first step in assimilation involves coordination of dinitrogen to one or two metal centers (the actual number has not yet been established). They may be the same or different (*e. g.* M = M′ = Mo or M = Mo, M′ = Fe) and in the resting phase, *i.e.* in the absence of dinitrogen, they probably exist as aquo complexes. Presumably, the oxidation state of the metal centers changes during reduction of the dinitrogen, *e. g.*

$L_xM^0 \rightarrow L_xM^I$ or L_xM^{II}

the reduced forms of the N_2 molecule possibly existing in deprotonated form, *e.g.* diimine as monoanion $[:\ddot{N}=\ddot{N}H]^{\ominus}$. Which of the steps postulated in the scheme have so far been verified *in vitro*?

1) Coordination of gaseous dinitrogen under physiological conditions is possible [*e.g.* eqs. (7)—(10)]. In the complexes isolated so far the dinitrogen is invariably bound in the end-on and never in the side-on mode.

2) Displacement of the end-product NH_3 by N_2 can be reproduced *e.g.* according to eq. (19).

3) Hydrazine complexes are well known. In addition, hydrazine is formed in the reduction of gaseous nitrogen with $V^{2\oplus}$ salts in alkaline solution[76] and by the hydrolysis of the Fe—N_2 and Ti—N_2 complexes mentioned in Section 5.4. The most conclusive argument for hydrazine as an intermediate, however, is probably the synthesis of the $[MCl_2(N_2H_2)(diphos)_2]$ (M = Mo, W) complexes according to eq. (27).

4) In Scheme 2, diimine complexes are postulated as intermediate stages. Until recently diimine was only known as an unstable intermediate, *e.g.* in organic hydrogenations with hydrazine, or as the decomposition product of HN_3, N_2H_4, or alkali metal tosylhydrazides at low temperatures (*ca.* −196 °C)[77–80]. Lately, however, it has been stabilized under normal conditions by complexation in [*trans*-$N_2H_2\{C_5H_5Mn(CO)_2\}_2$] and [*cis*-$N_2H_2\{Cr(CO)_5\}_2$].

These complexes are formed by the oxidation of hydrazine complexes[81,82]:

$$[C_5H_5Mn(CO)_2N_2H_4] \xrightarrow[-20\,^\circ C]{H_2O_2/Cu^{2\oplus}/THF} [trans\text{-}N_2H_2\{C_5H_5Mn(CO)_2\}_2] + [C_5H_5Mn(CO)_2N_2] + [C_5H_5Mn(CO)_2NH_3] \quad (28)$$

$$[\{(CO)_5Cr\}_2N_2H_4] + H_2O_2 \xrightarrow[Na_2SO_4/0^\circ C]{Cu^{2\oplus}/THF\cdot HCl} [cis\text{-}N_2H_2\{Cr(CO)_5\}_2] \quad (29)$$

The *trans* and *cis* structures of the diimine in the manganese and chromium complexes respectively are readily deduced from their IR spectra. The IR spectrum of [*cis*-$N_2H_2\{Cr(CO)_5\}_2$] is particularly clear. Since the typical absorptions of the $Cr(CO)_5$ groups are confined to the 2100—1800 and 800—350 cm^{-1} regions, bands outside these regions can be safely assigned to the N_2H_2 ligand vibrations. From group theory considerations, three IR-active vibrations ν_{as}(NH), δ_{as}(HNNH), and τ(HNNH) are anticipated for *trans*-N_2H_2, but five IR-active vibrations for *cis*-diimine [ν_{as} and ν_s(NH), δ_{as} and δ_s(HNNH), and ν(N=N)].

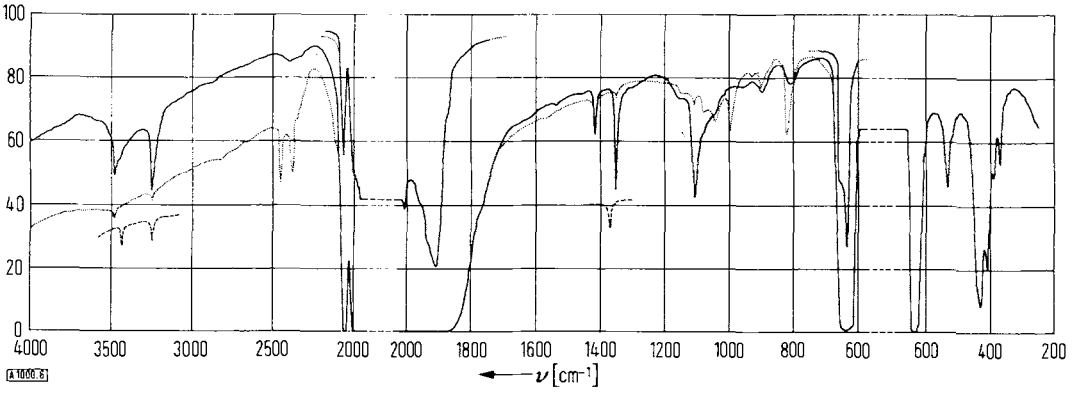


Figure 6. IR spectra (KBr) of $[N_2H_2\{Cr(CO)_5\}_2]$, ... $[N_2D_2\{(Cr(CO)_5\}_2]$, and $[^{15}N_2H_2\{Cr(CO_5\}_2]$ (only those regions that change compared with the spectrum of the N_2H_2 complex).

A glance at the IR spectrum of $[N_2H_2\{Cr(CO)_5\}_2]$ (Fig. 6) immediately shows that in the regions involved (4000—2100 and 1800—800 cm^{-1}) there are five absorptions, which in itself points to a *cis* structure for N_2H_2. Deuterium and ^{15}N-labeling confirm that the absorptions are in fact due to N_2H_2 vibrations and allow assignment of the absorption to vibrational forms of the diimine. Thus, it is seen that *e.g.* the absorption at 1415 cm^{-1} can only be due to the N—N stretching vibration, which, however, might be coupled to the Cr—N stretching vibrations[84].

What is extremely surprising in the synthesis of the diimine complexes is the fact that the tungsten-diimine complex also occurs in the *cis* form, although it is best prepared from the mononuclear hydrazine complex[85]:

$$[(CO)_5WN_2H_4] + H_2O_2 \xrightarrow[Na_2SO_4/0°C]{Cu^{2\oplus}/THF} [cis\text{-}N_2H_2\{W(CO)_5\}_2] + \text{by-products} \quad (30)$$

This could signify that in the complex *cis*-diimine is thermodynamically more stable than *trans*-diimine. A decision as to which of the two isomers is more stable in the free state has so far been impossible, both experimentally and by calculation[86]. The preferential formation of the *cis*-diimine complexes in the case of chromium and tungsten gains importance by the fact that reduction of substrates by nitrogenases most probably also proceeds stereospecifically in the *cis* position; thus, the reduction of C_2D_2 yields exclusively *cis*-deuterioethylene. As, furthermore, the diimine complexes undergo redox reactions under mild conditions in which N_2, N_2H_4, and NH_3 complexes are formed, they are suitable models for studying the intermediate stages in N_2 assimilation; just as the likely synchronous abstraction of two H atoms converts the binuclear chromium-hydrazine complex into the diimine complex, so the synchronous addition of two hydrogen atoms to a binuclear dinitrogen complex could reduce the latter to a *cis*-diimine complex.

7. Outlook for the Future

The first seven years of N_2 complex chemistry were marked by the search for new N_2 complexes and the failure to reduce the dinitrogen bound in them. Very recently a new development has begun to emerge. Now that it has been demonstrated experimentally that complex-bound dinitrogen can be reduced under relatively mild conditions and all the reduction states of the N_2 molecule have been identified, the prospects of finding a catalyst system allowing *in vitro* reproduction of the processes occurring in N_2 assimilation under mild conditions appear brighter than ever before.

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[1] Selection of earlier reviews: a) *A. D. Allen, R. O. Harris, B. R. Loescher, J. R. Stevens,* and *R. N. Whiteley*, Chem. Rev. *73*, 11 (1973); b) *J. Chatt* and *G. J. Leigh*, Chem. Soc. Rev. *1*, 121 (1972); c) *J. Chatt* and *R. L. Richards* in *J. R. Postgate:* The Chemistry and Biochemistry of Nitrogen Fixation. Plenum Press, London 1971, p. 57; d) *G. Henrici-Olivé* and *S. Olivé*, Angew. Chem. *81*, 679 (1969); Angew. Chem. internat. Edit. *8*, 650 (1969); e) *Yu. G. Borodko* and *A. E. Shilov*, Russ. Chem. Rev. *38*, 355 (1969).

[2] *A. D. Allen* and *C. V. Senoff*, Chem. Commun. *1965*, 621.

[3] *H. Bortels*, Arch. Mikrobiol. *1*, 333 (1930).

[4] a) International Union of Pure and Applied Chemistry: Nomenclature of Inorganic Chemistry, Butterworths, London 1970; b) *K. Jonas*, Angew. Chem. *85*, 1051 (1973); Angew. Chem. internat. Edit. *12*, 997 (1973); *C. Krüger* and *Y.-H. Tsay*, Angew. Chem. *85*, 1051 (1973); Angew. Chem. internat. Edit. *12*, 998 (1973).

[5] *G. C. Dobinson, R. Mason, G. B. Robertson, R. Ugo, F. Conti, D. Monelli, S. Cenini,* and *F. Bonati*, Chem. Commun. *1967*, 739.

[6] *W. H. Knoth*, J. Amer. Chem. Soc. *88*, 935 (1966).

[7] *J. K. Burdett, M. A. Graham,* and *J. J. Turner*, J. C. S. Dalton Trans. *1972*, 1620.

[8] *H. Huber, E. P. Kündig, M. Moskovits,* and *G. A. Ozin*, J. Amer. Chem. Soc. *95*, 332 (1973).

[9] *A. J. Rest*, J. Organometal. Chem. *40*, C76 (1972).

[10] *D. Sellmann* and *G. Maisel*, Z. Naturforsch. *27b*, 465 (1972).

[11] *D. Sellmann* and *G. Maisel*, Z. Naturforsch. *27b*, 718 (1972).

[12] *M. Hidai, K. Tominari, Y. Uchida,* and *A. Misono*, Chem. Commun. *1969*, 1392; *T. A. George* and *C. D. Seibold*, Inorg. Chem. *12*, 2544, 2548 (1973).

[13] *M. Aresta* and *A. Sacco*, Gazz. Chim. Ital. *102*, 755 (1972).

[14] *M. L. H. Green* and *W. E. Silverthorn*, J. C. S. Dalton Trans. *1973*, 301.

[15] *B. Bell, J. Chatt,* and *G. J. Leigh*, Chem. Commun. *1970*, 842.

[16] *D. Sellmann*, Angew. Chem. *83*, 1017 (1971); Angew. Chem. internat. Edit. *10*, 919 (1971).

[17] *D. Sellmann*, J. Organometal. Chem. *36*, C27 (1972).

[18] *J. Chatt, J. R. Dilworth,* and *G. J. Leigh*, Chem. Commun. *1969*, 687; cf. also *M. E. Tully* and *A. P. Ginsberg*, J. Amer. Chem. Soc. *95*, 2042 (1973).

[19] *J. Chatt, J. R. Dilworth,* and *G. J. Leigh*, J. Organometal. Chem. *21*, P49 (1970).

[20] a) *J. Chatt, J. R. Dilworth, H. P. Gunz, G. J. Leigh,* and *J. R. Sanders*, Chem. Commun. *1970*, 90; b) *J. Chatt, J. R. Dilworth,* and *G. J. Leigh*, J. C. S. Dalton Trans *1973*, 612; c) *J. Chatt, G. A. Heath,* and *G. J. Leigh*, J. C. S. Chem. Comm. *1972*, 444; d) J. Organometal. Chem. *57*, C67 (1973).

[21] *A. Sacco* and *M. Aresta*, Chem. Commun. *1968*, 1223.

[22] *G. M. Bancroft, M. J. Mays,* and *B. E. Prater*, Chem. Commun. *1969*, 589.

[23] *W. H. Knoth*, J. Amer. Chem. Soc. *90*, 7172 (1968).

[24] *P. G. Douglas, R. D. Feltham,* and *H. G. Metzger*, Chem. Commun. *1970*, 889.

[25] *A. D. Allen, F. Bottomley, R. O. Harris, V. P. Reinsalu,* and *C. V. Senoff*, J. Amer. Chem. Soc. *89*, 5595 (1967).

[26] *L. A. P. Kane-Maguire, P. F. Sheridan, F. Basolo,* and *R. G. Pearson*, J. Amer. Chem. Soc. *90*, 5295 (1968).

[27] *Y. G. Borodko, A. K. Shilova,* and *A. E. Shilov*, Dokl. Akad. Nauk SSSR *176*, 1297 (1967).

[28] *B. Bell, J. Chatt,* and *G. J. Leigh*, Chem. Commun. *1970*, 576.

[29] *J. Chatt, G. J. Leigh,* and *R. L. Richards*, J. Chem. Soc. *A 1970*, 2243.

[30] *J. Chatt, D. P. Melville,* and *R. L. Richards*, J. Chem. Soc. *A 1971*, 895.

[31] *A. D. Allen* and *J. R. Stevens*, Chem. Commun. *1967*, 1147.

[32] *H. A. Scheidegger, J. N. Armor,* and *H. Taube*, J. Amer. Chem. Soc. *90*, 3263 (1968).

[33] *G. Speier* and *L. Marko*, Inorg. Chim. Acta *3*, 126 (1969).

[34] a) *A. Sacco* and *M. Rossi*, Chem. Commun. *1969*, 471; b) *A. Yamamoto, S. Kitazume, L. S. Pu,* and *S. Ikeda, ibid. 1967*, 73.

[35] *M. Aresta, C. F. Nobile, M. Rossi,* and *A. Sacco*, Chem. Commun. *1971*, 781.

[36] *L. Y. Ukhin, A. Y. Shvetsov,* and *M. L. Khidekel*, Isv. Akad. Nauk SSSR, Ser. Khim. *1967*, 957.

[37] *J. P. Collman, M. Kubota, F. D. Vastine, J. Y. Sun,* and *J. W. Kang*, J. Amer. Chem. Soc. *90*, 5430 (1968).

[38] *S. C. Srivastava* and *M. Bigorgne*, J. Organometal. Chem. *18*, P30 (1969).

[39] a) *Yu. G. Borodko, I. N. Ivleva, L. M. Kachapina, S. I. Salienko, A. K. Shilova,* and *A. E. Shilov*, J. C. S. Chem. Comm. *1972*, 1178; b) *J. E. Bercaw, R. H. Marvich, L. G. Bell,* and *H. H. Brintzinger*, J. Amer. Chem. Soc. *94*, 1219 (1972); c) *E. E. van Tamelen, W. Cretney, N. Klaentschi,* and *J. S. Miller*, J. C. S. Chem. Comm. *1972*, 481; d) cf. also *J. H. Teuben*, J. Organometal. Chem. *57*, 159 (1973).

[40] *J. Chatt, J. R. Dilworth, G. J. Leigh,* and *R. L. Richards*, Chem. Commun. *1970*, 955; cf. also *J. Chatt, R. H. Crabtree, E. A. Jeffery,* and *R. L. Richards*, J. C. S. Dalton Trans. *1973*, 1167.

[41] *W. E. Silverthorn*, Chem. Commun. *1971*, 1310.

[42] *Yu. G. Borodko, M. O. Broitman, L. M. Kachapina, A. E. Shilov*, and *L. Yu. Ukhin*, Chem. Commun. *1971*, 1185.

[43] *D. F. Harrison, E. Weissberger*, and *H. Taube*, Science *159*, 320 (1968).

[44] *C. Creutz* and *H. Taube*, Inorg. Chem. *10*, 2664 (1971).

[45] *A. D. Allen*, Section Lecture, XIII[th] Intern. Conf. Coord. Chem., Zakopane 1970.

[46] *R. M. Magnusson* and *H. Taube*, J. Amer. Chem. Soc. *94*, 7213 (1972).

[47] *P. W. Jolly* and *K. Jonas*, J. Organometal. Chem. *33*, 109 (1971).

[48] Tables of Interatomic Distances *etc.*, Special Publications No. 11 and No. 18 of the Chemical Society, London 1958, 1965.

[49] *F. Bottomley* and *S. C. Nyburg*, Acta Crystallogr. *B 24*, 1289 (1968).

[50] *J. E. Fergusson, J. L. Love*, and *W. T. Robinson*, Inorg. Chem. *11*, 1662 (1972).

[51] *B. R. Davis* and *J. A. Ibers*, Inorg. Chem. *9*, 2768 (1970).

[52] *B. R. Davis* and *J. A. Ibers*, Inorg. Chem. *10*, 578 (1971).

[53] *B. R. Davis, N. C. Payne*, and *J. A. Ibers*, Inorg. Chem. *8*, 2719 (1969).

[54] *T. Uchida, Y. Uchida, M. Hidai*, and *T. Kodoma*, Bull. Chem. Soc. Jap. *44*, 2883 (1971).

[55] *J. M. Treitel, M. T. Flood, R. E. March*, and *H. B. Gray*, J. Amer. Chem. Soc. *91*, 6512 (1969).

[56] *R. Nast* and *H. Köhl*, Chem. Ber. *97*, 207 (1964).

[57] *G. Herzberg*: Molecular Spectra and Molecular Structure I. 2nd Edit. van Nostrand, Inc., Princeton 1955, p. 551.

[58] *M. A. I. Al-Joboury, D. P. May*, and *D. W. Turner*, J. Chem. Soc. *1965*, 616; *D. W. Turner* and *D. P. May*, J. Chem. Phys. *45*, 471 (1966).

[59] *R. S. Mulliken*, Can. J. Chem. *36*, 10 (1958).

[60] *C. Edmiston* and *K. Ruedenberg*, J. Chem. Phys. *43*, S 97 (1965).

[61] *K. G. Caulton, R. L. De Kock*, and *R. F. Fenske*, J. Amer. Chem. Soc. *92*, 515 (1970).

[62] *G. J. Leigh, J. N. Murrel, W. Bremser*, and *W. G. Proctor*, Chem. Commun. *1970*, 1661.

[63] *P. Finn* and *W. L. Jolly*, Inorg. Chem. *11*, 1434 (1972).

[64] *J. Chatt, D. P. Melville*, and *R. L. Richards*, J. Chem. Soc. *A 1969*, 2841.

[65] *A. D. Allen, T. Eliades, R. O. Harris*, and *V. P. Reinsalu*, Can. J. Chem. *47*, 1605 (1969).

[66] *D. J. Darensbourg*, Inorg. Chem. *10*, 2399 (1971).

[67] a) *J. Chatt, R. C. Fay*, and *R. L. Richards*, J. Chem. Soc. *A 1971*, 702; b) *M. Mercer, R. H. Crabtree*, and *R. L. Richards*, J. C. S. Chem. *1973*, 808.

[68] *D. E. Harrison* and *H. Taube*, J. Amer. Chem. Soc. *89*, 5706 (1967).

[69] *J. Chatt, G. J. Leigh*, and *R. L. Richards*, J. Chem. Soc. *A 1970*, 2243.

[70] a) *C. M. Elson, J. Gulens*, and *J. A. Page*, Can. J. Chem. *49*, 207 (1971); b) *A. Yamamoto, S. Kotazume, L. S. Pu*, and *S. Ikeda*, J. Amer. Chem. Soc. *89*, 3071 (1967).

[71] *J. N. Armor* and *H. Taube*, J. Amer. Chem. Soc. *92*, 2560 (1970).

[72] a) *M. W. Bee, S. F. A. Kettle*, and *D. B. Powell*, J. C. S. Chem. Comm. *1972*, 767; b) *J. E. Bercaw, E. Rosenberg*, and *J. D. Roberts*, J. Amer. Chem. Soc. *96*, 612 (1974).

[73] *G. D. Watt*, J. Amer. Chem. Soc. *94*, 7351 (1972).

[74] *J. Chatt, G. A. Heath*, and *R. L. Richards*, J. C. S. Chem. Comm. *1972*, 1010.

[75] Cf. [1c], pp. 89, 90, and 101 as well as [1b].

[76] *A. Shilov, N. Denisov, O. Efimov, N. Shuvalov, N. Shuvalova*, and *A. Shilova*, Nature *231*, 460 (1971); cf. also *G. N. Schrauzer, P. A. Doemeny, R. H. Frazier*, and *G. W. Kiefer*, J. Amer. Chem. Soc. *94*, 7378 (1972).

[77] *S. N. Foner* and *R. L. Hudson*, J. Chem. Phys. *28*, 719 (1958).

[78] *K. Rosengren* and *G. C. Pimentel*, J. Chem. Phys. *43*, 507 (1965).

[79] *A. Trombetti*, Can. J. Phys. *46*, 1005 (1968).

[80] *N. Wiberg, H. Bachhuber*, and *G. Fischer*, Angew. Chem. *84*, 889 (1972); Angew. Chem. internat. Edit. *11*, 829 (1972).

[81] *D. Sellmann*, J. Organometal. Chem. *44*, C 46 (1972).

[82] *D. Sellmann, A. Brandl*, and *R. Endell*, J. Organometal. Chem. *49*, C 22 (1973).

[83] *G. A. Heath, R. Mason*, and *K. M. Thomas*, J. Amer. Chem. Soc. *96*, 259 (1974).

[84] *D. Sellmann, A. Brandl*, and *R. Endell*, Angew. Chem. *85*, 1122 (1973); Angew. Chem. internat. Edit. *12*, 1019 (1973).

[85] *D. Sellmann, A. Brandl*, and *R. Endell*, Angew. Chem. *85*, 1121 (1973); Angew. Chem. internat. Edit. *12*, 1019 (1973).

[86] Cf. *J. Alster* and *L. A. Burnelle*, J. Amer. Chem. Soc. *89*, 1261 (1967); *L. J. Schaad* and *H. B. Kinser*, J. Phys. Chem. *73*, 1901 (1969); *L. Radan, W. J. Hehre*, and *J. A. Pople*, J. Amer. Chem. Soc. *93*, 289 (1971).

The Helicenes

By Richard Henri Martin[*]

"Helicene" is the name introduced by *Newman* in 1955, to describe the benzologues of phenanthrene in which the extra *ortho*-condensed rings give rise to a (regular) cylindrical helix. The pioneer work of *Newman* in this field cannot be overemphasized; his brillant synthesis and resolution of [6]helicene, achieved eighteen years ago, will remain as a landmark, for it opened the way to the study of a fascinating class of synthetic molecules. In the following review, an attempt is made to summarize the present state of our knowledge in this rapidly expanding field.

1. Introduction

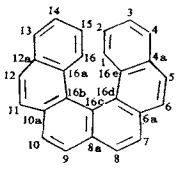
The helicenes are characterized by a helical structure made up of *ortho*-condensed aromatic rings, by the presence of a powerful inherently chiral chromophore, and by the possibility of interactions (*e.g.* electronic interactions) between overlapping aromatic rings. The scientific interest raised by these compounds is due to the unique combination of these three properties in a single molecule.

We shall deal first with the nomenclature of these compounds. The "class name" is "helicene"; "carbohelicenes" contain only carbon atoms in the skeleton, "heterohelicenes" at least one hetero-aromatic ring. In this review helicenes that are made up of benzene rings only are referred to as "all-benzene-helicenes"[**]. "Double helicenes" are helicenes containing

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[**] *Editorial note*: The expression "benzo-helicenes" is unsuitable, since the prefix "benzo" denotes, according to IUPAC rule A-21.4, the annelation of a benzene ring. The expressions "benzoid helicenes" or "benzenoid helicenes" could be misunderstood for the terms "benzoid" and "benzenoid" are usually used in the sense of "benzene-like" and/or "aromatic".

two distinct helicene structures which can be either of the same or of opposite helicity. In "bihelicenyls", two helicenyl residues are coupled by a single bond. For the sake of simplicity we shall adopt *Newman*'s suggestion for the numbering of the helicene skeletons [see formula *(1)*].



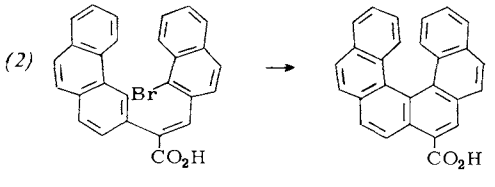
(1)

Individual carbo- and hetero-helicenes can be systematically named in accordance with the IUPAC rules A-21 and A-22, and B-3 or B-4, respectively. In the case of all-benzene-helicenes, a frequently used alternative nomenclature indicates the number of rings present in a compound by an arabic numeral (in square brackets) preceding the name "helicene". Thus compound *(1)*, phenanthro[3,4-*c*]phenanthrene, is called [6]helicene. The number of all types of rings can also be designated by multiplying affixes; *e.g.* compounds *(1)* and *(15)* (see below) are hexahelicenes. The name "hexahelicene", however, is frequently used for "[6]helicene".

A large number of heterohelicenes, in which some of the benzene rings are replaced by thiophene rings, have been synthesized and studied at the University of Groningen, Holland. The fundamental contribution of *Wynberg, Groen et al.* in this field (photosyntheses, resolution, rates of racemization, determination of the absolute configuration of these systems and the study of their chiroptical, spectral and chemical properties *etc.*) have been so well described in a concise and stimulating review published by *Wynberg* in 1971[2], that it is felt justifiable here to focus our main attention on the more recent work that has been carried out in this field and, wherever possible, to draw the readers attention to the close similarities or striking differences observed in the properties of the all-benzene- and hetero-helicenes.

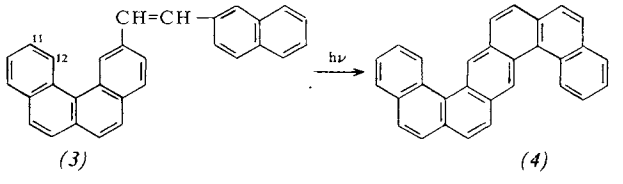
2. Synthetic Problems

The first synthesis of an all-benzene-helicene, if we exclude [4]- and [5]helicene, is the well known twelve step synthesis of [6]helicene described by *Newman* and *Lednicer*[1]. The main advantage of the very elegant synthetic scheme used by these authors is its unambiguity; it is therefore particularly unfortunate that all attempts to use this scheme for the preparation of the higher benzologue [7]helicene, remained unsuccessful. The second synthesis of [6]helicene was achieved eleven years later by *Bogaert-Verhoogen* and *Martin*[3]. The crucial step of this synthesis is the potash fusion of *(2)* leading to [6]helicene-8-carboxylic acid in 44% yield. This last scheme has recently been used to prepare [7]helicene-7-carboxylic acid,

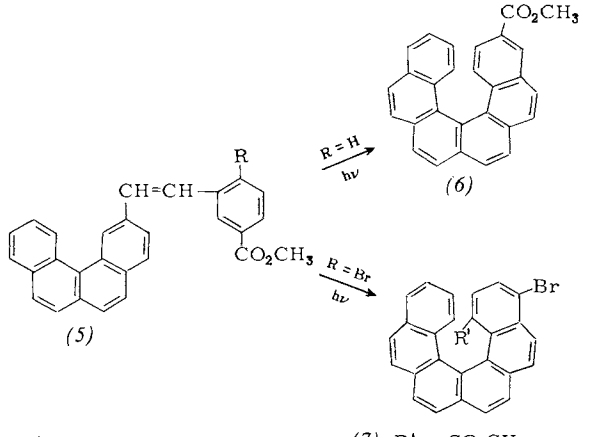


(2)

in relatively low yield (*D. Bogaert-Verhoogen*[4]). Both of these schemes suffer from serious limitations[10]; the breakthrough came when it was found that the helicenes could be prepared in fair to excellent yields by the photoinduced cyclodehydrogenation of appropriate 1,2-diarylethylenes[5], following the procedure described by *Wood* and *Malory* in 1964 for the preparative scale photoconversion of stilbene to phenanthrene[6]. It was at the same time surprising and very exciting indeed to discover that the photocyclization process which could give rise to many isomers, in particular to fully planar polycyclic aromatic hydrocarbons, could be of preparative interest for the synthesis of the helicenes! Even more startling is the fact that, in most cases, the helicene is the only cyclized product observed. The photocyclization of *(3)*, which leads preferentially to *(4)*, is one of the most striking exceptions[7]. In such cases, the formation of the undesired product can be either fully or largely prevented by the introduction of a bromine atom as illustrated in Scheme 1. When R = H, methyl [6]helicene-3-carboxylate *(6)* is the major product; on the other hand, when R = Br, the main product is methyl 4-bromo[6]helicene-1-carboxylate *(7)* from which [6]helicene-1-methanol can be prepared in one step by $LiAlH_4$ reduction (*K. Le Van* and *J. Jespers*[4]). In the helicene field, photocyclization has proven exceptionally rewarding. In the course of a few years numerous helicenes of all types, including double helicenes and heterohelicenes, have been prepared, mainly by *Wynberg et al.* (Groningen), by *Laarhoven et al.* (Nijmegen), and in our own laboratory (Brussels)[*]. (For reviews on the photocyclization of stilbene analogs see Refs. [8, 9].)



(3) *(4)*



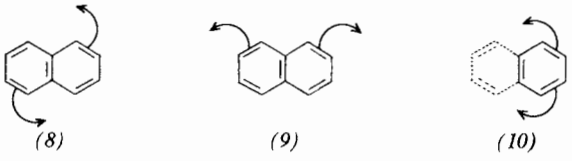
Scheme 1

(7), R' = CO_2CH_3

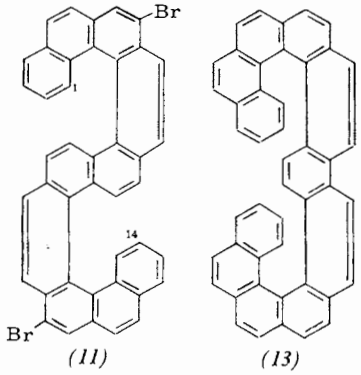
The photocyclization process is extremely simple. The required 1,2-diarylethylenes or bis(arylvinyl)arenes can usually be prepared, in excellent yields, either by the Wittig reaction or

[*] A few problems encountered in the synthesis of all-benzene-helicenes are critically discussed in Ref. [10]. On p. 123 of this review, instead of 1-azahexahelicene, read 3-azahexahelicene.

by the Siegriest reaction[11]. Because of the well known *cis*-⇌*trans* photoequilibrium, the stereochemistry of the starting material is unimportant. Double photocyclizations have proved very useful in many cases, as illustrated by the two-step synthesis of [6]helicene[12], the preparation of [13]-[13], [11]-, [12]-, and [14]helicene (*M. Baes*[4]), and by the synthesis of double helicenes[14] and heterohelicenes[86b]. Substituted all-benzene-helicenes can be prepared without difficulty if the substituent is already present in the molecule to be cyclized; acetyl, dimethylamino and nitro groups are however excluded[9]. An interesting carbohelicene containing a biphenylene system (biphenyleno[2,3-*a*]pentahelicene) has been synthesized recently by *Figeys* and *Vanommeslaeghe*[16]. So far, three types of all-benzene double helicenes, *(8)*, *(9)*, and *(10)*, have been prepared. When the two helicene structures have the same number of rings, *meso* and *dl* pairs are to be expected. If the two helices are up-up (or down-down) in *(11)* and up-down in *(12)* and *(13)*, the corresponding compounds are *dl* pairs. In the case of *(11)*, two stereoisomers have indeed been isolated. The fact that the higher melting isomer was shown to give a positive nuclear Overhauser effect (NOE) between H^1 and H^{14} (proximity effect) proves its *dl* structure[14b].

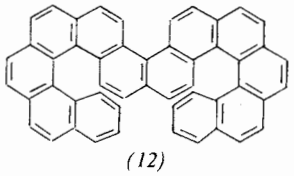


(8) *(9)* *(10)*



(11)

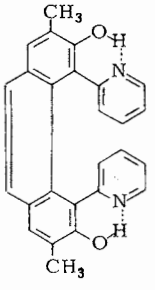
(13)



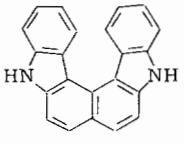
(12)

According to *Laarhoven*[17], the isolated stereoisomer of *(12)* is probably the *dl* pair. In the case of structure *(13)* (*C. Eyndels*[4] and *W. H. Laarhoven*[17]) space-filling models indicate that the *meso* form is sterically very unfavorable. An X-ray diffraction study carried out by *J. Dunitz* (Zurich)[17] on our compound and the partial resolution observed by *Laarhoven* have indeed shown that the only stereoisomer obtained is the *dl* pair. An attempt, by *H. Kagan et al.*[17] to demonstrate the *dl* nature of the higher melting isomer of *(11)* by an absolute asymmetric synthesis using circularly polarized light has unfortunately proven unsuccessful.

4-Aza- *(47c)*[18], 1-aza-, 2-aza- *(47a)* and 3-aza[6]helicene *(47b)*, 2-aza[7]helicene and 2-aza[8]helicene have been prepared by *M. Deblecker* and *F. Geerts-Evrard*[14]. The bromide of 4a-azonia[6]helicene, characterized by NMR spectroscopy but not isolated in a pure state, and the bromides of 4a- and 6a-azonia[4]helicene, have been prepared photochemically by the procedure used by *Bradsher*[19] for the synthesis of azoniaphenanthrenes (*V. Libert* and *H. P. Vanroux*[4]). A number of interesting compounds involving intramolecular hydrogen bonds [*e.g. (14)*], formally related to the azoniahelicenes, have been described recently[15]. As already mentioned, numerous heterohelicenes containing thiophene rings, including a hetero-undecahelicene[51], have been photosynthesized by *Wynberg et al.*[*]. Heterohelicenes containing a furan ring[20] and carbazole systems[21] have been prepared by other methods. Among these, *(15)* is interesting from the historical point of view for, as far as we are aware, this was the first hexahelicene ever synthesized[21b].



(14)

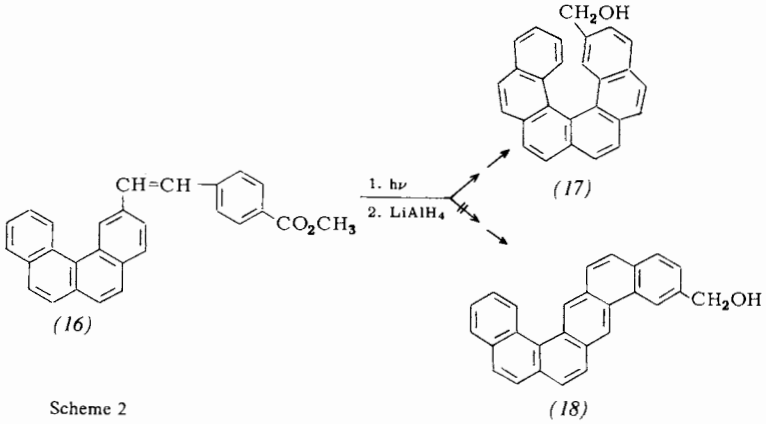


(15)

3. Structural Determinations

As already pointed out, the photocyclization of 1,2-diarylethylenes and bis(arylvinyl)arenes can in principle give rise to many structural isomers. Thus, the double photocyclization used for the synthesis of [13]helicene could give ten cyclized isomers[13]. In contrast, there is usually no ambiguity associated with the photochemical syntheses of heterohelicenes carried out by *Wynberg et al.*

The structural determinations are therefore of crucial importance in the all-benzene-helicene and azahelicene series. How-



(16) *(17)* *(18)*

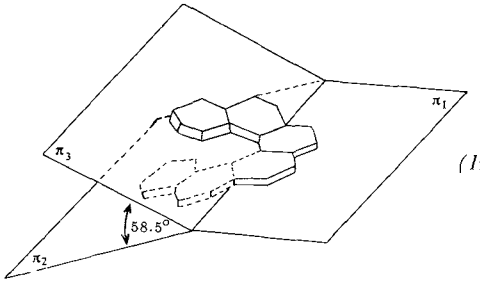
Scheme 2

[*] The first photosyntheses of all-benzene-helicenes and heterohelicenes were carried out simultaneously and independently in Brussels and in Groningen respectively in 1967.

ever with our increasing knowledge of the properties of the helicenes, this problem can usually be solved without difficulty. NMR spectroscopy has of course been particularly useful in this respect; but other techniques have been applied with success—*e.g.* X-ray diffraction, independent syntheses, specific deuterium labeling[22], GLC[23], study of chiroptical properties, *etc.* The use of a property associated (in this case) with chirality is illustrated in Scheme 2. The structure of the cyclized product was confirmed by the NMR spectrum of the corresponding alcohol [6]helicene-2-methanol *(17)*, which showed an AB system for the diastereotopic protons of the methylene group, thus excluding structure *(18)*.

4. Conformations of Helicenes in the Solid State

So far, relatively few X-ray diffraction studies have been carried out in the helicene series. The first X-ray crystal structure analysis of a (hetero)helicene was published by *Stulen* and *Visser* in 1969[24]. Since then, the 1:1 complex [6]helicene/4-bromo-2,5,7-trinitrofluorenone[25], 2-bromo- and 2-methyl[6]helicene[26,27], and [6]helicene itself[28] have been studied by this technique. As already mentioned, the stereochemistry of a double helicene has been elucidated by X-ray diffraction. Of the helicenes in which there is complete overlap of aromatic rings, only 11-bromo[9]helicene (*J. Jespers*[4]) has been examined so far (*G. W. Frank*[17]). [6]Helicene can be roughly depicted by three planes as shown in *(19)*.



(19)

The interplanar angle between the terminal rings is 58.5°. The average bond length for the six inner core carbon-carbon bonds is 1.437 ± 0.004 Å, while the bonds parallel to these on the periphery have an average bond length of 1.334 ± 0.007 Å. The close agreement between the predicted and the observed distortions from coplanarity in [6]helicene, is a welcome tribute to the pioneer work of *Coulson* in this field[29]. Figure 1 gives an idea of the spatial architecture of [13]helicene.

As pointed out by *Lightner et al.*: "... groups no more bulky than a bromine atom or a methyl group when substituted onto carbon 2 and 15 do not significantly alter the geometry of the helix by steric interaction"[27]. The shortest C—C contacts (≈ 3 Å) are always between carbon atoms separated by five bonds *e.g.* C^1 and C^{16a} in 2-methyl[6]helicene and C^1 and C^{22c} in 11-bromo[9]helicene: "This implies that in an infinite helicene molecule there are only $5^1/_2$ benzene rings per helix turn" (*G. W. Frank*[17]). A dramatic change in the shape of the helicene skeleton has however been observed recently by *Laarhoven et al.*[17] in the case of 1,16-dimethyl[6]-helicene. This change is reflected in the much smaller interplanar angle between the terminal rings: 29.6° versus 58.5° in [6]helicene[*]!

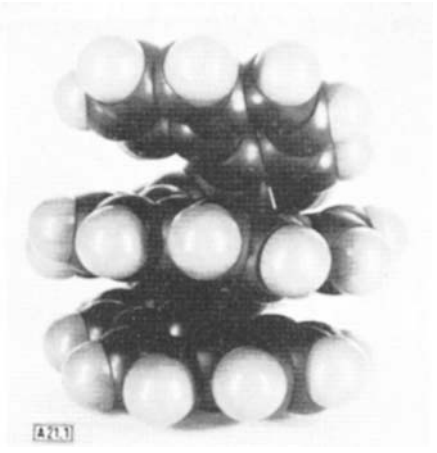
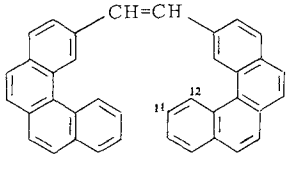


Fig. 1. Space-filling model of [13]helicene.

5. Conformation of Helicenes and Helicene Precursors in Solution

Laarhoven et al. have studied the influence of bulky substituents introduced in C^1 and C^2 of [6]helicene, on the UV and NMR spectra[30]. These authors concluded that the helical structure is only appreciably modified by the presence of a large substituent (*e.g. tert*-butyl) in C^1. Polarographic data (half-wave potentials) collected by *Laarhoven* and *Brus*[31] for eight helicenes, including benzo[6]helicenes, indicate that the compounds examined deviate to a similar degree from coplanarity. ^{1}H-NMR studies of the conformation in solution of the *cis*-1,2-diarylethylenes used in the photochemical synthesis of the all-benzene-helicenes, have been carried out independently by *Martin et al.*[32] and by *Laarhoven et al.*[33]. The spectra of these compounds are, in many respects, strongly reminiscent of the spectra of the corresponding all-benzene-helicenes. Thus *e.g.* the strong high field shifts of H^{11} and H^{12} in *cis-(20)* versus *trans-(20)*, the specific solvent effects,



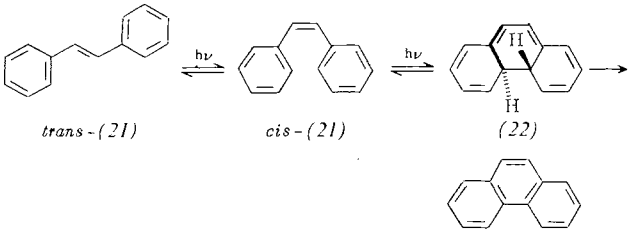
(20)

the influence of tris(2,2,6,6-tetramethyl-3,5-heptanedionato)-praseodymium on the chemical shift of these protons and the temperature dependence of the resonances, clearly indicate the importance of the contribution of "helicene-like" conformations in solution at room temperature. In view of the fact that the geometry in the relaxed excited state may be very different from the geometry in the ground state, there is no obvious correlation between this observation and the ease of photocyclization to the helicene structures. Indeed, *cis-(3)*—whose protons H^{11} and H^{12} show the largest up-field shifts in the unsubstituted series—is one of the few 1,2-diarylethylenes, which does not give the helicene structure ([7]helicene) preferentially!

[*] The conformations in the solid state of a number of *cis*-1,2-diarylethylenes used as precursors in the photosynthesis of all-benzene-helicenes, have been determined by X-ray diffraction (*G. Tsoucaris* [17] and *H. Rabinovich* [17]).

6. The Mechanism of the Photocyclization

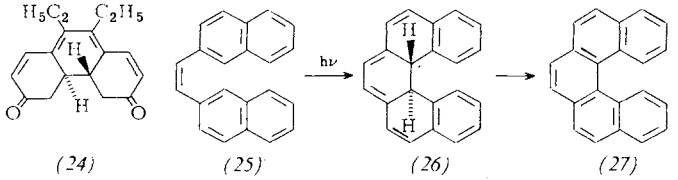
The photocyclodehydrogenation in solution of *cis*-stilbene and its analogues is a very complex process which will require further extensive research to be fully understood. Intensive research into this problem has been carried out at the Weizmann Institute (*Fischer, Muszkat, Bromberg et al.*[34]) and at other laboratories[35, 36, 40, 46, 89]. The complexity of the problem is clearly illustrated by the following quotation[34h]: "The common method employed for photocyclodehydrogenation reactions to obtain phenanthrene derivatives involves UV irradiation in the presence of air and iodine. In view of the present results, it appears plausible that under these conditions the DHP's (dihydrophenanthrenes) produced primarily are dehydrogenated by a combination of processes including spontaneous oxidation with molecular oxygen and iodine, oxidation with atomic iodine, and oxidation involving electronically-excited DHP. It is unlikely that singlet oxygen is also involved, in view of the absence of reports on similar dehydrogenation reactions . The recent developments in this field will not be summarized here; however, the stereochemistry of the dihydro intermediates and the regioselectivity will be briefly discussed. The general reaction pathway of the photocyclization of stilbene is outlined in Scheme 3.



trans-(21) *cis*-(21) (22) (23)

Scheme 3

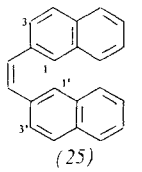
Until quite recently, no unambiguous proof of the (*trans*-)stereochemistry of the dihydro-intermediates of such reactions was available, the major difficulty arising from the fact that these intermediates could not be isolated. However, in the case of the photocyclization of diethylstilboestrol, *Doyle et al.*[37] have isolated a stable dihydro-tautomer *(24)* of the primary cyclization product. By ozonolysis of this intermediate, *Laarhoven et al.*[38] have isolated *dl*-butane-1,2,3,4-tetracarboxylic acid, thus proving the *trans* configuration of the dihydro-intermediate. This elegant demonstration implies a conrotatory process, as predicted by the Woodward-Hoffmann rules for a concerted photocyclization in the S_1 state. An



(24) (25) (26) (27)

ingenious and decisive proof that the photocyclization of the unsubstituted *cis*-1,2-diarylethylene leading to [5]helicene *(27)* is also a conrotatory process, followed soon after. 1,2-Bis(2-naphthyl)ethylene *(25)* was chosen because of the exceptional thermal stability of the corresponding dihydro[5]helicene *(26)*[39, 34l][*]. By using right and left handed circularly polarized light for the cyclization, *Goedicke* and *Stegemeyer*[40] isolated the optically active (excess (−) and (+), respectively) *trans*-14b,14c-dihydro[5]helicene *(26)*, thus achieving an absolute asymmetric synthesis of this intermediate. As it was already known that the first excited singlet state of the *cis*-1,2-diarylethylene is involved in this type of reaction[41], it followed that the cyclization does not involve "hot" ground state molecules as reactive species.

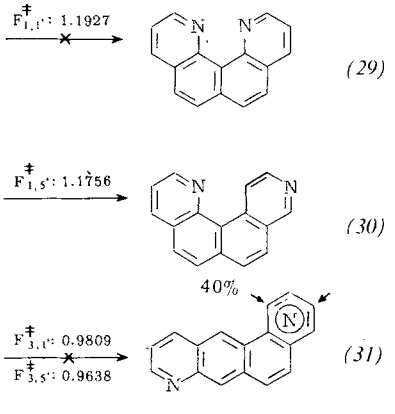
$F_r^{\ddagger}$
1: 0.630
3': 0.452



$L_{r,s}^{\ddagger}$
1,1' = 2.922
3,1' = 3.281
3,3' = 3.622

(25)

The precise origin of the *regioselectivity* of the photocyclizations is yet another unsettled fundamental problem. In 1967, *Scholz et al.*[42] found that the photocyclizations leading to tetra- and pentacyclic all-benzene-hydrocarbons [*e.g. (25)*] take place almost exclusively between the *(ortho)* carbon atoms showing the highest value of free valence indices in the first excited state ($F_r^{\ddagger}$) or the smallest localization energy ($L_{r,s}^{\ddagger}$)[**]. In the course of the following years, *Laarhoven et al.*, *Timmons et al.*, and *Martin et al.* in collaboration with *Figeys*, made extensive use of this observation either to confirm or to predict the regioselectivity of numerous photocyclizations—including photocyclizations leading to azahelicenes. As shown by *Laarhoven et al.*[43], the photocyclodehydrogenations only take place if the sum of the free-valence indices for the atoms between which cyclization could occur is greater than unity ($\Sigma F_{r,s}^{\ddagger} > 1$). This simple "exclusion-rule" has been further ela-



borated to deal with cases in which more than one $\Sigma F_{r,s}^{\ddagger}$ is greater than unity (products ratio) and to account for steric factors (formation of planar versus non-planar polycyclic aromatic systems)[44]. The usefulness of these empirical rules

[*] Quantum yields [34l] for the following processes have been reported: *cis-(25)*→*(26)*: 0.01; *(26)*→*cis-(25)*: 0.005; *cis*-stilbene→dihydrophenanthrene: 0.1; *(22)*→*cis*-stilbene ≈ 0.7. It is interesting to note that *Fischer* [17] has been unable to observe the photoformation of a dihydro-intermediate by irradiation of 1,2-bis(3-phenanthryl)ethylene.

[**] $L_{r,s}^{\ddagger} = \pi$ electron energy of the starting material in the first excited state minus the π electron energy of the dihydro intermediate in the ground state.

from the synthetic point of view has been demonstrated in a number of publications (see *e.g.* Ref. [45]). It is interesting to note that the photocyclization of *(28)* failed to give 1,12-diaza[4]helicene *(29)*, in spite of the high value of the corresponding $F_{r,s}^{+}$. This result can be ascribed to repulsive interactions between the lone pairs of the nitrogen atoms along the reaction path leading to *(29)* (*F. Geerts-Evrard*[41])[*].

Failure of 1,2-diarylethylenes to cyclize on electron impact (M−2 mass lines of relative abundance smaller than 5%) has also been correlated by *Blackburn* and *Timmons*[46] with the failure of such compounds to photocyclize with aromatization. The converse need not be the case.

7. Chiroptical Properties

With the exception of the double helicenes and bihelicenyls in their *meso* forms, the helicenes are inherently chiral molecules. The unsubstituted all-benzene-helicenes belong to point group C_2; they are dissymmetric and palindromic[**].

7.1. Optical Resolution

The first experimental proof of the chirality of a helicene was given by *Newman, Lutz,* and *Lednicer*[47] in 1955. Their brilliant resolution of [6]helicene was accomplished using an optically active π-complexing agent (TAPA)[***] specially synthesized for this purpose.

Three monosubstituted [6]helicenes have been resolved so far: the 7-trimethylphosphoniomethyl[6]helicene ion *via* its D(−)hydrogendibenzoyltartrates[48], [6]helicene-2-carboxylic acid by column chromatography of its menthyl ester (*V. Libert*[4]), and 2-bromo[6]helicene with TAPA[26]. One of the heterohelicenes containing carbazole systems has been partially resolved into enantiomers by column chromatography on acetylated cellulose[21c].

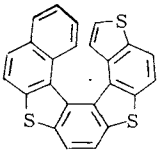
In the course of our work on [7]helicene, (the late) *G. M. J. Schmidt* drew our attention to the fact that our specimen of this hydrocarbon had crystallized in the non-centrosymmetric space group $P2_1$. Knowing from the work of *Newman* that [6]helicene has an exceptionally high optical activity ($[\alpha]_D^{24} = 3640°$), it was at once clear that optical activity due to the formation of a conglomerate should be detectable by "hand-picking" of just *one* crystal of [7]helicene.

This proved to be the case. *M. Barbieux*, who had carried out the first synthesis of [7]helicene, grew crystals which were all optically active, one of them being even optically pure: $[\alpha]_D^{20} = 6200 \pm 200°$[7,49]. The formation of optically pure crystals seems to be exceptional in the all-benzene-helicene and heterohelicene series, probably on account of microtwinning.

Since then, [6]-, [8]- and [9]helicene[49], as well as a number of heterohelicenes[50,2] have been "partially resolved" by this technique[*]. On the other hand, we have been unable, so far, to detect the existence of conglomerates in the case of the higher benzologues of [9]helicene and of monosubstituted all-benzene-helicenes[**].

These unsuccessful attempts may have been due to different reasons: the microsize of the crystals, the difficulty to grow single crystals and, last but not least, the failure to find the proper solvent. In this connection, we wish to recall the observation made by *Wynberg et al.*[51] that *dl-(32)* can be "partially resolved" by crystallization from optically active (−)-α-pinene. It has however not been established yet "whether this resolution is thermodynamic in nature or simply due to preferential seeding (kinetic) or to a combination of both".

To our knowledge, the crystallization of *dl-(32)* from the enantiomeric (+)-α-pinene has not yet been attempted. A partial photoinduced destructive kinetic resolution of [6]helicene, using circularly polarized light, has been described by *Kagan et al.*[52] *(vide infra)*. It should be mentioned that optically active all-benzene-helicenes and heterohelicenes can be prepared by homologation of an optically active precursor. Thus, *Wynberg et al.*[51] have obtained a dextrorotatory undecaheterohelicene starting from partially resolved (+)-*(32)*. We are presently working on the synthesis of a series of optically active all-benzene-helicenes, using optically active [6]helicene-2-carboxylic acid as the precursor. This synthetic scheme has already been tested without prior resolution; *dl*-[8][53], [9]-, [10]- and [11]helicene have thus been prepared in 40%, 74%, 79%, and 45% yields, respectively (*V. Libert*[4]). The chirality of the helicene molecule can of course be detected by X-ray crystallography (determination of space group or full crystal structure analysis), ^{1}H-NMR spectroscopy (*e.g.*, diastereotopic protons in [6]helicene-2-methanol *(17)*[53]), ^{13}C-NMR spectroscopy (*e.g.*, diastereotopic $^{13}CH_3$ in 2-isopropyl[6]helicene[30])[***] *etc.* *Oosterhoff*'s attempt to use the "circular polarization of luminescence" technique[54] in the all-benzene-helicenes has unfortunately failed so far[17].



(32)

7.2. Optical Purity

The only helicenes whose $[\alpha]_{max}$ values are presently known are [6]-[11], [7]-, [8]- and [9]helicene[49], 2-bromo[6]helicene[26], and 7-methyl[6]helicene[48]. (Rotation values in chloroform:

[*] When the yield of the cyclized product(s) is relatively low, no conclusion should be drawn from the study of the $F_{r,s}^{+}$, for it is clear that some of the cyclized isomers, particularly those with an anthracene structure, could be "photodestroyed" selectively.

[**] For a musical palindrome cf. *J. Haydn*: 47th Symphony, 3rd part "Menuet al Roverso" (1772)!

[***] TAPA = 2-(2,4,5,7-tetranitro-9-fluorenylideneaminooxy)propionic acid.

[*] This "hand-picking" procedure is based, like the famous technique of *Pasteur*, on the formation of conglomerates. However, in the helicene series, because of the very high optical activities, the crystals of the two enantiomers need not be distinguishable. Only the sign of rotation of the solutions of each individual crystal has to be determined; needless to say, this is a time-consuming preparative scale procedure which requires a tremendous amount of perseverance.

[**] *Frank et al.* [27], however, have observed by X-ray diffraction that crystals of 2-methyl[6]helicene grown from the racemic mixture (benzene-pentane) are optically pure.

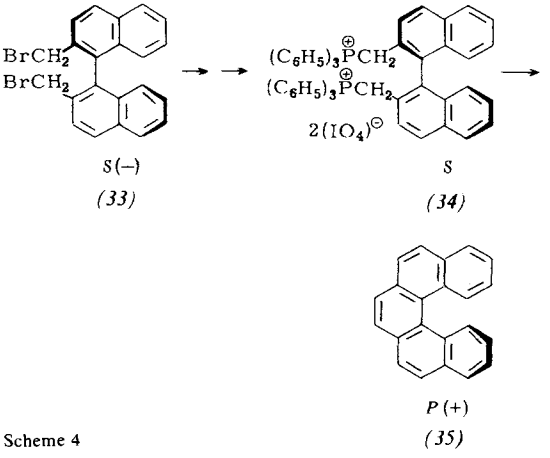
[***] The values 55.2 and 55.5 ppm quoted for $\delta^{13}CH_3$ in Ref. [30] are in error and should read 53.7 and 54.0 ppm upfield from $CHCl_3$. We apologize for this mistake which was due to a transitory technical deficiency of our instrument.

$[\alpha]_D^{24} = 3640 \pm 10°$, $[\alpha]_{579}^{25} = 5900 \pm 200°$, $[\alpha]_{579}^{25} = 6900 \pm 200°$, $[\alpha]_{579}^{25} = 8100 \pm 200°$, $[\alpha]_{579}^{25} = 3560°$, and $[\alpha]_D = 3157°$, respectively.) The unsubstituted all-benzene-helicenes were partially resolved by "spontaneous resolution" and further purified by repeated crystallizations under non-equilibrium conditions. The final purification was achieved by two "normal" crystallizations.

7.3. Absolute Configuration

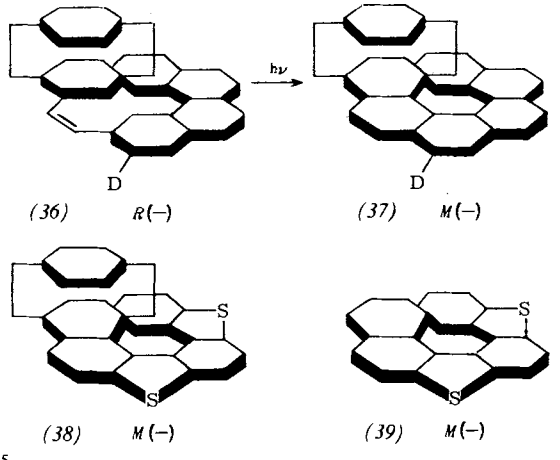
The assignment of the absolute configuration of the helicenes has only been settled recently. Three distinct lines of approach have been used to solve this problem: calculations performed to relate the sign of the long wavelength optical activity to the stereochemistry (helicity) of the molecule, X-ray diffraction studies using Bijvoet's method, and chemical assignments. The most recent and sophisticated treatments (π-SCF orbitals) of the long wavelength optical activity of the all-benzene-helicenes, carried out independently by *Mason et al.*[55] and by *Wagnière et al.*[56], both lead to the conclusion that the dextrorotatory helicenes have the right-handed (*P*) helicity[*]. This conclusion was confirmed a few months later by an X-ray diffraction study (anomalous X-ray scattering) of (−)-2-bromo[6]helicene performed by *Lightner et al.*[26]. The protodebromination of (−)-2-bromo[6]helicene yielded levorotatory [6]helicene. It is appropriate to recall at this point that the first assignment of the absolute configuration of a helicene was achieved by *Wynberg et al.*[58], by X-ray diffraction, on a heterohelicene whose thiophene rings provided the required heavy atom. The results obtained by these authors, namely that (−)-*(39)* has the left-handed helicity, was correctly predicted beforehand by *Groen*[59]. X-ray studies have thus shown that the levorotatory all-benzene-helicenes and heterohelicenes have the same left-handed (*M*) configuration.

The challenge to determine the absolute configuration of helicenes by chemical correlations was tackled simultaneously and independently by *Bestmann et al.*[60] and by *Martin et al.*[62]. *Bestmann*'s elegant and simple method for the determination of the absolute configuration of [5]helicene is shown in Scheme 4[*].



Scheme 4

Tribout and *Martin* used (−)-[2,2]paracyclophane-4-carbaldehyde (Scheme 5) of known absolute configuration as starting material for the synthesis of the levorotatory substituted helicene *(37)* ($[\phi]_{578}^{25} = -12464° \pm 100°$) which, for compelling steric reasons can only have the left-handed (*M*) configuration. The authors then concluded from the close similarity between the ORD and CD curves of this "(−)-[2,2]paracyclophanohelicene" *(37)* and (−)-[6]helicene ($[\phi]_{578}^{25} = -12300°$) that both have the same (*M*) helicity. An application of the above scheme in the heterohelicene series, carried out in collaboration with *Doyle* and *Wynberg*[62], provided a rigorous proof of the validity of the method. Thus the ORD curve of the "(−)-[2,2]paracyclophanoheterohelicene" *(38)* showed overall similarities with the ORD curve of the corresponding (−)-heterohelicene *(39)*, whose left-handed configuration had been determined by X-ray diffraction[59] (Scheme 5).



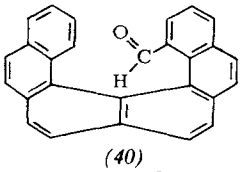
Scheme 5

7.4. Chemically Induced Asymmetric Syntheses

Only preliminary unpublished results are presently available in this field.

7.4.1. Asymmetric Syntheses Induced by the Helicene Skeleton

We have recently observed that the reduction of *dl*-[6]helicene-1-carbaldehyde (abbreviation: [6]-1-CHO) *(40)* with $LiAlD_4$ gives essentially one *dl* pair of the diastereomeric monodeuteriated alcohols (in the ratio 96:4). The *reversed* ratios of the diastereomeric alcohols is obtained by reduction of the deuteriated aldehyde with $LiAlH_4$. Reoxidation with DDQ[**], of the alcohols resulting from the $LiAlH_4$ reduction gives a 96:4 mixture of 1-CDO- and 1-CHO[6]helicene.



≡ [6]-1-CHO

(40)

[6]-1-CHO $\xrightarrow{LiAlH_4}$ [6]-1-CH_AH_BOH

[6]-1-CHO $\xrightarrow{LiAlD_4}$ [6]-1-$\overset{*}{C}H_ADOH$

[6]-1-CDO $\xrightarrow{LiAlH_4}$ [6]-1-$\overset{*}{C}DH_BOH$

[*] As early as 1957, *Moscowitz* [57] using simple Hückel π molecular orbitals arrived at the opposite conclusion. It is important to note in this connection that no sign inversion had inadvertently occurred, as was believed at one time ([58], foot-note 9). The discrepancy is essentially due to the fact that *Moscowitz* could not include configuration interaction among the thirty lowest excited singlets. What is remarkable is that the absolute magnitudes and shapes of his calculated curves so closely approximate the experimental data of *Newman et al.* [74], despite the sign discrepancy (*A. J. Moscowitz*, personal communication).

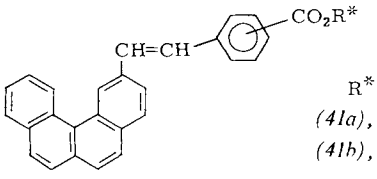
[*] Bestmann's oxidative coupling of phosphonium salts is the simplest preparative scale procedure yet available for the synthesis of *dl*-[5]helicene [61].

[**] DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

We believe, from NMR evidence, that the most favorable conformation of [6]helicene-1-carbaldehyde is the one shown in *(40)*. If so, the main alcohol resulting from the $LiAlD_4$ reduction of the right-handed (*P*) aldehyde probably has the (*R*) configuration [(*M*)aldehyde→(*S*)alcohol (*J. Jespers*[4]).

7.4.2. Asymmetric Syntheses of All-Benzene-Helicenes Induced by Chiral Substituents[*]

The photocyclizations of the (−)-menthyl esters *(41a)* and *(41b)*, followed by complete reduction ($LiAlH_4$) of the unpurified reaction products, yielded (−)-[6]helicene-3- and -2-methanol respectively.



R* = (−)−Menthyl
(41a), *meta* $-CO_2R^*$
(41b), *para* $-CO_2R^*$

The optical yields of these reactions are not yet known (*J. Jespers* and *V. Libert*[4]); further work is in progress, in collaboration with *K. Mislow*.

7.5. Absolute Asymmetric Synthesis Using Circularly Polarized Light

A century ago, *Le Bel*[63] clearly pointed out that the use of (left- or right-handed) circularly polarized light must, in principle, induce "absolute asymmetric syntheses"[**]. Ever since, numerous attempts have been made to carry out such syntheses, but in no case published before 1971 was there compelling evidence in favor of success; in fact, when the reactions were repeated recently, the claimed asymmetric *syntheses* could not be confirmed. The practical difficulties were such that the possibility of achieving an absolute asymmetric synthesis was even seriously questioned[64]. In order to solve this problem, it was essential to discover a photochemical reaction for which the *g* factor[***] of the chiral precursor (at a given wavelength) and/or the magnitude of the $[\alpha]_{max}$ of the final product are favorable. Such is the case in the photoinduced cyclodehydrogenation of certain 1,2-diarylethylenes leading to all-benzene-helicenes. In this reaction, the relatively small *g* factor of the chiral precursor is well compensated by the exceptionally high optical rotation of the helicene, as was demonstrated by *Kagan et al.*[52,65] and independently by *Calvin et al.*[66]. It is highly satisfactory to note that: a) the optical rotations of the final products are highly significant (no possible ambiguity), b) the helicenes prepared from right and left-handed circularly polarized light show opposite signs of rotation, and c) the photoinduced destructive kinetic resolution of [6]helicene is much slower than its induced photosynthesis and leads to optical activities of opposite signs. The fact that the observed optical activity is not due to an induced asymmetric transformation of the dihydro-intermediate has been confirmed by both schools. *Calvin et al.* have further shown, in the case of [8]helicene, that the optical yield and the sign of rotation of the final product is strongly dependent on the wavelength of the circularly polarized light used for irradiation.

These absolute asymmetric syntheses are only possible because the enantiomers of the helicene precursors (*cis*-1,2-diarylethylenes)—which absorb circularly polarized light of a given chirality to slightly different extents ($\varepsilon_R \neq \varepsilon_S$)—are in *rapid interconversion* at room temperature. Experiments designed to better understand the reason of the large differences observed in the optical yields of closely related helicene syntheses, have been described by *Buchardt et al.*[67]. It is interesting to note in this connection that the double photocyclizations of bis(arylvinyl) arenes of the type Ar′—CH=CH—Ar—CH=CH—Ar′ (Ar′ = or ≠Ar) show in some cases extremely low or undetectable optical yields[*]; such is the case, for example, in the photosyntheses of the double helicene *(11)* (light circularly polarized at 313 nm) and of [13]helicene (light circularly polarized at 313 nm and, in another experiment, at 380 nm). The reason for this observation is not yet clear and further work is in progress. An absolute asymmetric synthesis of 1-aza[6]helicene has been achieved recently by *Kagan*[17].

7.6. Thermal Racemizations

If the above "absolute asymmetric syntheses" using circularly polarized light constitute one of the major contributions to the helicene studies, then the thermal racemization of [7]-, [8]- and [9]helicene is undoubtedly the most surprising and intriguing discovery in this field[68,69][**]. Kinetic data of the thermal racemization in solution of [5]-[70], [6]-, [7]-, [8]- and [9]helicene[69] are listed in Table 1.

Table 1. Kinetic data for the thermal racemization of some helicenes in solution.

Helicene	[5]	[6]	[7]	[8]	[9]
$\Delta H^{\neq}$ [kcal mol^{-1}]	22.9	35.0	40.5	41.0	41.7
$\Delta S^{\neq}$ [cal mol^{-1} deg^{-1}]	−4.1	−4.2	−3.9	−4.6	−6.1
$\Delta G^{\neq}$ [kcal mol^{-1}] (27 °C)	24.1	36.2	41.7	42.4	43.5
E_a [kcal mol^{-1}] (27 °C)	23.5	35.6	41.1	41.6	42.3
$t_{1/2}$ (rac.) [min] (T [°C])	62.7 (57)	13.4 (221.7)	13.4 (295)	31 (293.2)	123 (293.5)

[*] The first reported *chemically induced asymmetric synthesis of an all-benzene-helicene skeleton* is the photocyclization of *(36)* leading to *(37)*.

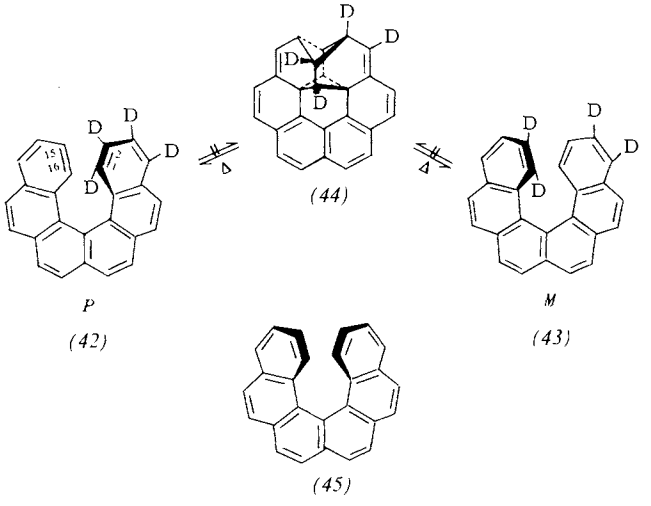
[**] It is common practice to use the expression: "absolute asymmetric syntheses" to describe those asymmetric syntheses which are induced by a chiral *physical* agent instead of by a chiral *chemical* reagent. This distinction, although convenient, is in no way fundamental.

[***] The optical anisotropy factor *g* is defined as the ratio of the circular dichroism $\Delta\varepsilon$ to the extinction coefficient ε.

[*] *H. Kagan et al.* and *R. H. Martin et al.*, unpublished results.

[**] With the exception of [13]helicene, no higher all-benzene-helicene has yet been even partially resolved. Brief accounts or kinetic studies on the thermal racemization of [5]helicene[70], [6]helicene[11], heterohelicenes[71], 2,2′-bi[6]helicenyl[72] and diphenanthro[3,4-*c*:3′,4′-*l*]chrysene[14a] have been published; however, prior to our work, no helicene in which the terminal rings facially overlap had been studied from this point of view.

It should be noted that the $\Delta G^{\neq}$ values for [7]-, [8]- and [9]helicene are remarkably similar. Three reaction pathways have been considered for these racemizations: 1. bond breaking; 2. reaction path involving an internal double Diels-Alder adduct (suggested by *J. Nasielski*); 3. conformational pathway[69]. The first hypothesis, namely the complete rupture of a C—C bond with the formation of a non-stabilized diradical is hardly compatible with the kinetic results. As for the second hypothesis, in the case of [6]- and [7]helicene the occurrence of an internal double Diels-Alder adduct [*(44)* in Scheme 6] has been experimentally discarded by the study of appro-



Scheme 6

priate substituted derivatives. The inversion of the helix by way of an internal double Diels-Alder reaction would be accompanied, in the case of [6]helicene, by a permutation of (D)H—C^1—C^2—H(D) versus H—C^{16}—C^{15}—H. No such permutation was however observed when *dl*-[1,2,3,4-D_4]-[6]helicene *(42)* was submitted to prolonged racemization conditions. The third hypothesis, the "conformational pathway", seems to be the most reasonable one at the present time. The "relatively" low potential barriers for these racemizations can be justified in the conformational process by the fact that the necessary molecular deformations (bond torsion, bond bending *etc.*) are spread over a large number of bonds. This process does not require an achiral conformation along the inversion path; however a non-planar achiral conformation, such as *(45)*, may well occur in the racemization of the unsubstituted all-benzene-helicenes[*].

If, as we believe, the thermal racemization of the helicene is a conformational process, it then follows that the non-planar polycyclic aromatic hydrocarbons in general and the helicenes in particular, are dramatically more flexible than expected. As pointed out earlier by the present author, this erroneous belief is probably largely due to the common use of rigid models, particularly space-filling models... These models which are invaluable in many respects, have however serious shortcomings which may be difficult to assess correctly. Although all-benzene-helicenes are photolabile, they do not racemize photochemically.

[*] In 1968, *Dougherty* [73] stated that the thermal racemization of [6]helicene "requires that the molecule twist through a symmetrical conformation", thus implying a conformational process for the racemization of this hexanuclear helicene.

7.7. ORD, CD and MCD

The CD curve of [5]helicene[70] and the ORD and CD curves of [6]-[74], [7]-, [8]- and [9]helicene[49] and a number of heterohelicenes[75] have been recorded. These curves clearly show that the all-benzene-helicenes of a given series (levo or dextro) have the same helicity. The same is true in the heterohelicene series of *Wynberg*[2]. *Weigang* and *Trouard-Dodson*[76] have studied the CD spectrum of [6]helicene in glasses at liquid nitrogen temperature. The MCD curves of *dl*-[6] to [9]helicene have been recorded by *Djerassi*[17]. It is unfortunate that the ORD and CD curves of the chiral double all-benzene-helicenes are not yet known, for it would be interesting to compare the optical properties of these compounds with the optical properties of the isomeric "normal" all-benzene-helicenes.

8. Spectral Properties

8.1. ^{1}H-NMR Spectroscopy

^{1}H-NMR spectroscopy has played a very important part in the researches carried out on the helicenes in recent years. The structure of practically every all-benzene-helicene, synthesized by the photocyclization process, has been deduced from its ^{1}H-NMR spectrum[*]. The C_2 symmetry of the (unsubstituted) all-benzene-helicenes, has been of great help in this connection, not only in ^{1}H-NMR but also in ^{13}C-NMR spectroscopy[22]. Of particular interest to us was the study of the repercussions of the progressive overlap of benzene rings on the chemical shifts of the protons of the underlying ring(s)[77]. As expected, these protons are shifted to higher fields by the induced diamagnetic ring-current of the overlapping benzene ring(s). The annelation process affects successively the protons of the ABCD four-spin system and of the two-spin systems (EF, GH...) in a rather regular way[**]. This work has now been extended to the higher benzologues, up to [14]helicene (*M. Baes* and *N. Defay*[41])[***].

Some of the protons of the all-benzene-helicenes, from [6]helicene onwards, also show specific solvent effects (C_6D_6 versus $CDCl_3$) which distinguish them from the less distorted isomers which can be formed in the photocyclizations. *Haig* and *Mallion*[78] have carried out a thorough and accurate study of the ^{1}H-NMR spectra of [4]-, [5]- and [6]helicene and have extended the Hückel-London-McWeeny theory of "ring current" effects on proton chemical shifts to non-planar aromatic systems. *Defay*[79], using the very powerful INDOR technique, has not only assigned practically every transition of the ^{1}H-NMR spectrum of [7]helicene, but has also revealed the existence of positive $^5J_{tt}$ (epi) and negative $^4J_{cc}$ (peri) long range cross-ring couplings in this molecule.

Use of the INDOR technique has moreover yielded important information on the double all-benzene-helicene series. *Figeys*

[*] It is a particular pleasure for me to take this opportunity to express my deepest gratitude to a long standing and enthusiast collaborator, Dr. *Nicole Defay*, whose original NMR contributions to our researches in the field of polycyclic aromatic systems, including the helicenes, has been invaluable.

[**] Cf. Figures 7 and 8 in Ref. [77].

[***] The dramatic improvement of the NMR technique in the course of the last 18 years is well illustrated by recalling the conclusion of a study of the NMR spectrum of [6]helicene carried out in 1956: "There does not appear to be any sizable effect due to the 'helical type' overlap of the rings" [1].

et al., *Wynberg et al.*, and *Laarhoven et al.* have also carried out extensive work on the ^{1}H-NMR spectra of helicenes containing a biphenylene ring system[16], heterohelicenes[2], substituted helicenes[30, 16], benzo[6]helicene[80], double helicenes[14] *etc.*

8.2. ^{13}C-NMR Spectroscopy

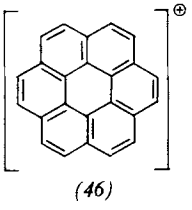
The ^{13}C-NMR spectra of [4]- to [7]helicene[81] have been fully assigned as far as the protonated carbon atoms are concerned. Specific deuterium labeling has been used in a few cases by *Martin et al.*[82] for assignment purposes in the all-benzene-helicene series. The observed *ortho* isotope high-field shifts are particularly useful for the specific assignment of the quaternary carbon atoms common to two rings.

Although evidence for the existence of diamagnetic ring current effects on the ^{13}C resonances has been obtained[83], these effects are concealed in most cases by other factors. ^{13}C-NMR spectroscopy is thus less suitable than ^{1}H-NMR spectroscopy as a probe for the magnetic properties of the cyclic π-system of the helicenes.

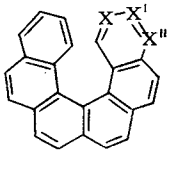
8.3. Mass Spectrometry

The mass spectrum of [6]helicene[73] shows a very intense peak at $m/e=300$ ($M-C_2H_4$) and an intense metastable ion corresponding to the $m/e=328\rightarrow m/e=300$ transition; it also shows peaks for doubly charged ions. There is evidence that the ion with $m/e=300$ is the coronene ion *(47)*[*]. The loss of C_2H_4 has also been observed by *Groen*[84] in the case of heteroheptahelicenes[**]. In order to explain the formation of [coronene]$^+$ from [[6]helicene]$^+$, *Dougherty* has postulated the formation of an internal Diels-Alder adduct, followed by the loss of ethylene. It is interesting to note that the stereochemistry of this adduct (supra-supra on the same side of the aromatic-strip to allow the subsequent loss of ethylene) is different from the stereochemistry of the first internal Diels-Alder adduct (supra-supra on opposite sides of the aromatic-strip) susceptible to lead to the double adduct *(44)* mentioned in our discussion of the racemization of the helicenes (Section 7.6).

The low resolution mass spectrum of 2-aza-[6]helicene *(47a)* has ions at $m/e=300$, 301, and 302; at a resolution of 40000, each of these show two peaks at $m/e=329-C_2H_5$ (10%) and $329-CNH_3$ (90% coronene?), at $329-C_2H_4$ (10%), and $329-CNH_2$ (90%), and at $329-C_2H_3$ (70% azoniacoronene?) and $329-HCN$ (30%); metastable ions are observed for the *m/e* 329→300, 329→301, and 329→302 transitions. Very similar observations have been made in the case of 3-aza- *(47b)* and 4-aza-[6]helicene *(47c)* except that the $M-HCN$ ion is missing (*M. Deblecker*[4]). The occurrence of ions corresponding to the mass of the coronene ion in the last two spectra, suggests that the coronene ion hypothesis should be further scrutinized. An investigation of some potentially pericyclic reactions in the mass spectrometer has been carried out by *Bishop* and *Flemming*[85].



(46)



(47a), X = N, X' = X'' = CH
(47b), X' = N, X = X'' = CH
(47c), X'' = N, X = X' = CH

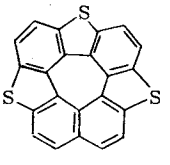
[*] Thermolysis of [6]helicene for 2h at 485°C (10^{-6} torr at 25°C) gives ethylene as the only product volatile at 0°C along with traces of coronene [73].

[**] The heterohexahelicenes of *Wynberg* and *Groen* do not have the right geometry to give the corresponding cyclized ions by loss of C_2H_4.

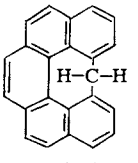
9. Chemical Reactions and Other Investigations

Substitution reactions involving unsubstituted all-benzene-helicenes are as yet unknown. In the case of heterohelicenes, lithiation *ortho* to the S atom of a terminal thiophene ring followed by formylation has been used by *Wynberg et al.*[51] for synthetic purposes.

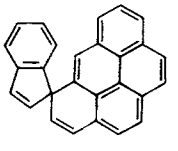
On treating a heterohexahelicene with $AlCl_3$—NaCl at 140°C *Wynberg et al.*[86] have observed the formation of a new C—C bond between the first carbon atoms of the terminal rings (loss of H_2). The product thus obtained has been used by these authors to synthesize the heterocirculene *(48)*, a member of an interesting new class of compounds. In the all-benzene-helicene series, *Martin et al.* have observed the formation of a methano bridge [cf. *(49)*] between the two end rings of [5]helicene on treatment of [5]helicene-1-methanol in acid medium (*Y. Cochez*[4]). On the other hand, a similar treatment of [6]helicene-1-methanol gave a high yield of product *(50)* (*J. Jespers*[4]). This rearrangement is the first example of a chemically induced modification of an all-benzene-helicene skeleton.



(48)



(49)

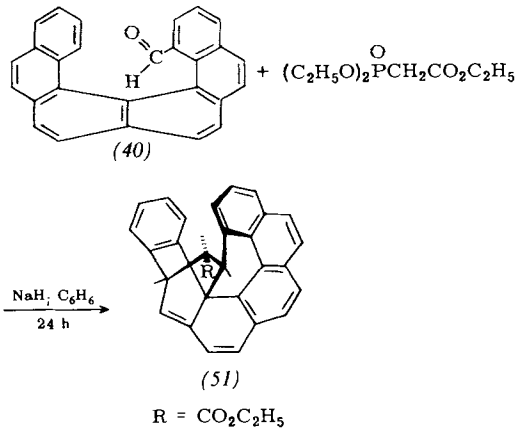


(50)

An interesting intramolecular [4+2]cycloaddition [*(40)*→*(51)*], involving the [6]helicene skeleton, has recently been discovered by the school in Brussels (*J. Jespers*[4]).

Only a limited number of further interesting studies carried out in the helicene field can be mentioned in the space available here. The question of σ-π mixing in helicenes has been discussed by *Moscowitz*[57a], *El-Sayed*[87], and, more recently, by *Wagnière*[56a] and *Mason*[55]. Experimental evidence of these interactions is however still lacking. The electron transfer between anion and molecule of [6]helicene and the optical and magnetic properties of anions of hexahelicene have been studied by *Weissman et al.*[88, 89]. The fluorescence of the *cis* and *trans* naphthylethylenes and the helicenes have been examined by *Fischer, Stegemeyer et al.*[90] and *Vander Donckt et al.*[91], respectively.

The study of the helicenes has already yielded important and unexpected results. It is our personal conviction that



(40)

(51)

R = $CO_2C_2H_5$

further work on these unique molecules, whose accessibility is no longer a serious problem, should be highly rewarding in many fields of chemistry.

Never before have I had a better opportunity to give full credit to all my co-workers for their very fine contribution to the study of the helicenes; I sincerely hope that they enjoyed this common venture as much as I did! I also wish to express my deepest gratitude to the Colleagues, in particular Professor H. Kagan and Professor H. Wynberg, and research workers of other laboratories who either collaborated with us or made us benefit from their experience. The financial support of our "helicene program" by the "Fonds de la Recherche Fondamentale Collective" is gratefully acknowledged.

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[1] *M. S. Newman* and *D. Lednicer*, J. Amer. Chem. Soc. *78*, 4765 (1956).

[2] *H. Wynberg*, Accounts Chem. Res. *4*, 65 (1971).

[3] *D. Bogaert-Verhoogen* and *R. H. Martin*, Tetrahedron Lett. *1967*, 3045.

[4] *R. H. Martin et al.*, unpublished work; the names of the collaborators are mentioned in the text.

[5] *M. Flammang-Barbieux*, *J. Nasielski*, and *R. H. Martin*, Tetrahedron Lett. *1967*, 743.

[6] *C. S. Wood* and *F. B. Mallory*, J. Org. Chem. *29*, 3373 (1964).

[7] *R. H. Martin*, *M. Flammang-Barbieux*, *J. P. Cosyn*, and *M. Gelbcke*, Tetrahedron Lett. *1968*, 3507.

[8] *F. R. Stermitz* in *O. L. Chapman*: Organic Photochemistry. M. Dekker, New York 1967, Vol. 1, p. 247.

[9] *E. V. Blackburn* and *C. J. Timmons*, Quart. Rev. Chem. Soc. *23*, 482 (1969).

[10] *R. H. Martin*, Aromaticity, Pseudo-Aromaticity, Anti-Aromaticity. The Jerusalem Symposia of Quantum Chemistry and Biochemistry, III. The Israel Academy of Sciences and Humanities, Jerusalem 1971, p. 115.

[11] a) *A. E. Siegrist* and *H. R. Meyer*, Helv. Chim. Acta *52*, 1282 (1969); b) *A. E. Siegrist*, *P. Liechti*, *H. R. Meyer*, and *K. Weber*, *ibid. 52*, 2521 (1969).

[12] *R. H. Martin*, *M. J. Marchant*, and *M. Baes*, Helv. Chim. Acta *54*, 358 (1971).

[13] *R. H. Martin*, *G. Morren*, and *J. J. Schurter*, Tetrahedron Lett. *1969*, 3683.

[14] a) *W. H. Laarhoven* and *Th. J. H. M. Cuppen*, Tetrahedron Lett. *1971*, 163; Rec. Trav. Chim. Pays-Bas *92*, 553 (1973); b) *R. H. Martin*, *Ch. Eyndels*, and *N. Defay*, Tetrahedron Lett. *1972*, 2731; c) *W. H. Laarhoven* and *M. H. De Jong*, Rec. Trav. Chim. Pays Bas *92*, 651 (1973).

[15] *D. L. Fields* and *T. Regan*, J. Org. Chem. *36*, 2991 (1971); J. Heterocyclic Chem. *10*, 195 (1973).

[16] *H. P. Figeys et al.*, Brussels, unpublished results.

[17] Private communication.

[18] *R. H. Martin* and *M. Deblecker*, Tetrahedron Lett. *1969*, 3597.

[19] *R. E. Doolittle* and *C. K. Bradsher*, Chem. Ind. (London) *1965*, 127; J. Org. Chem. *31*, 2616 (1966).

[20] *J. N. Chatterjea* and *K. D. Banerji*, J. Indian Chem. Soc. *47*, 576 (1970).

[21] a) *W. Fuchs* and *J. Niszel*, Ber. Deut. Chem. Ges. *60*, 209 (1927); b) *M. Zander* and *N. H. Franke*, Chem. Ber. *102*, 2728 (1969); c) *H. J. Teuber* and *L. Vogel*, *ibid. 103*, 3319 (1970).

[22] *R. H. Martin* and *J. J. Schurter*, Tetrahedron *28*, 1749 (1972); Tetrahedron Lett. *1969*, 3679.

[23] *J. F. Nicoud*, *A. Moradpour*, *G. Balavoine*, *H. Kagan*, *R. H. Martin*, and *M. Deblecker*, J. of Chromatogr. *66*, 43 (1972), cf. footnote on p. 48.

[24] *G. Stulen* and *G. J. Visser*, Chem. Comm. *1969*, 965.

[25] *I. R. Mackay*, *J. L. Robertson*, and *J. G. Sime*, Chem. Comm. *1969*, 1470.

[26] a) *D. A. Lightner*, *D. T. Hefelfinger*, *G. W. Frank*, *T. W. Powers*, and *K. N. Trueblood*, Nature Phys. Sci. *232*, 124 (1971); b) *D. A. Lightner*, *D. T. Hefelfinger*, *Th. W. Powers*, *G. W. Frank*, and *K. N. Trueblood*, J. Amer. Chem. Soc. *94*, 3492 (1972).

[27] *G. W. Frank*, *D. T. Hefelfinger*, and *D. A. Lightner*, Acta Crystallogr. *B 29*, 223 (1973).

[28] *C. de Rango*, *G. Tsoucaris*, *J. P. Declerq*, *G. Germain*, and *J. P. Putzeys*, Cryst. Struct. Comm. *2*, 189 (1973).

[29] *C. A. Coulson* and *S. Senet*, J. Chem. Soc. *1955*, 1819.

[30] *W. H. Laarhoven* and *R. C. M. Veldhuis*, Tetrahedron *28*, 1811 (1972).

[31] *W. H. Laarhoven* and *G. J. L. Brus*, J. Chem. Soc. *B 1971*, 1433.

[32] *R. H. Martin*, *N. Defay*, *H. P. Figeys*, *K. Le Van*, *J. J. Ruelle*, and *J. J. Schurter*, Helv. Chim. Acta *55*, 2241 (1972).

[33] *M. H. de Jong* and *W. H. Laarhoven*, Rec. Trav. Chim. Pays-Bas *92*, 675 (1973).

[34] a) *A. Bromberg* and *K. A. Muszkat*, J. Amer. Chem. Soc. *91*, 2860 (1969); b) *A. Bromberg*, *K. A. Muszkat*, and *E. Fischer*, Chem. Commun. *1968*, 1352; c) *A. Warshel* and *A. Bromberg*, J. Chem. Phys. *52*, 1262 (1970); d) *A. Bromberg*, *K. A. Muszkat*, and *A. Warshel*, *ibid. 52*, 5952 (1970); e) *A. Bromberg*, *K. A. Muszkat*, *E. Fischer*, and *F. S. Klein*, J. Chem. Soc. Perkin II *1972*, 588; f) *S. Sharafy* and *K. A. Muszkat*, J. Amer. Chem. Soc. *93*, 4119 (1971); g) *K. A. Muszkat* and *W. Schmidt*, Helv. Chim. Acta *54*, 1195 (1971); h) *T. Knittel-Wismonsky*, *G. Fischer*, and *E. Fischer*, Tetrahedron Lett. *1972*, 2853; i) *A. Bromberg*, *K. A. Muszkat*, and *E. Fischer*, Isr. J. Chem. *10*, 765 (1972); j) *A. Bromberg* and *K. A. Muszkat*, Tetrahedron *28*, 1265 (1972); k) *G. Fischer* and *E. Fischer*, Mol. Photochem. *3*, 373 (1972); l) *T. Knittel*, *G. Fischer*, and *E. Fischer*, J. C. S. Chem. Comm. *1972*, 84.

[35] *F. B. Mallory* and *C. W. Mallory*, J. Amer. Chem. Soc. *94*, 6042 (1972).

[36] a) *R. Srinivasan* and *J. N. C. Hsu*, J. Amer. Chem. Soc. *93*, 2816 (1971); b) *D. D. Morgan*, *S. W. Horgan*, and *M. Orchin*, Tetrahedron Lett. *1970*, 4347; c) *E. W. Blackburn* and *C. J. Timmons*, J. Chem. Soc. *C 1970*, 163.

[37] *Th. D. Doyle*, *N. Filipescu*, *W. R. Benson*, and *D. Banes*, J. Amer. Chem. Soc. *92*, 6371 (1970).

[38] *Th. J. H. M. Cuppen* and *W. H. Laarhoven*, J. Amer. Chem. Soc. *94*, 5914 (1972).

[39] *E. V. Blackburn*, *C. E. Loadner*, and *C. J. Timmons*, J. Chem. Soc. *B 1968*, 1156.

[40] *Ch. Goedicke* and *H. Stegemeyer*, Chem. Phys. Lett. *17*, 492 (1972).

[41] a) *H. Stegemeyer*, Z. Naturforsch. *17b*, 153 (1962); b) *F. B. Mallory*, *C. S. Wood*, and *J. T. Gordon*, J. Amer. Chem. Soc. *86*, 3094 (1964).

[42] *M. Scholz*, *M. Muhlstadt*, and *F. Dietz*, Tetrahedron Lett. *1967*, 665.

[43] *W. H. Laarhoven*, *Th. J. H. M. Cuppen*, and *R. J. F. Nivard*, Rec. Trav. Chim. Pays-Bas *87*, 687 (1968).

[44] *W. H. Laarhoven*, *Th. J. H. M. Cuppen*, and *R. J. F. Nivard*, Tetrahedron *26*, 4865 (1970).

[45] a) *H. H. Perkampus* and *Th. Blumm*, Tetrahedron *28*, 2099 (1972); b) *D. D. Morgan*, *S. W. Horgan*, and *M. Orchin*, Tetrahedron Lett. *1972*, 1789; c) *T. Sato* and *T. Morita*, Bull. Chem. Soc. Jap. *45*, 1548 (1972); d) *W. H. Laarhoven*, *Th. J. H. M. Cuppen*, and *R. J. F. Nivard*, Tetrahedron *26*, 1069 (1970); e) *Ch. Goedicke* and *H. Stegemeyer*, Ber. Bunsenges. *73*, 782 (1969); f) *K. A. Muszkat* and *S. Sharafi-Ozeri*, Chem. Phys. Lett. *20*, 397 (1973).

[46] *E. V. Blackburn* and *C. J. Timmons*, J. Chem. Soc. *C 1970*, 172.

[47] *M. S. Newman*, *W. B. Lutz*, and *D. Lednicer*, J. Amer. Chem. Soc. *77*, 3420 (1955).

[48] *M. S. Newman* and *Chin H. Chen*, J. Org. Chem. *37*, 1312 (1972).

[49] *R. H. Martin* and *M. J. Marchant*, Tetrahedron *30*, 343 (1974).

[50] *H. Wynberg* and *M. B. Groen*, J. Amer. Chem. Soc. *90*, 5338 (1968).

[51] *H. Wynberg* and *M. B. Groen*, J. Amer. Chem. Soc. *92*, 6664 (1970).

[52] *A. Moradpour*, *J. F. Nicoud*, *G. Balavoine*, *H. Kagan*, and *G. Tsoucaris*, J. Amer. Chem. Soc. *93*, 2353 (1971).

[53] *R. H. Martin* and *J. P. Cosyn*, Synth. Commun. *1*, 257 (1971).

[54] *H. P. J. M. Dekkers*, *C. A. Emeis*, and *L. J. Oosterhoff*, J. Amer. Chem. Soc. *91*, 4589 (1969).

[55] a) *A. Brown, C. M. Kemp*, and *S. F. Mason*, J. Chem. Soc. *A 1971*, 751; b) *W. S. Brickell, A. Brown, C. M. Kemp*, and *S. F. Mason, ibid. 1971*, 756.

[56] a) *G. Wagnière*, Aromaticity, Pseudo-Aromaticity, Anti-Aromaticity. The Jerusalem Symposium on Quantum Chemistry and Biochemistry, III. The Israel Academy of Sciences and Humanities. Jerusalem 1971; p. 127; b) *W. Hug* and *G. Wagnière*, Tetrahedron *28*, 1241 (1972).

[57] *A. J. Moscowitz*, Thesis Harvard 1957; Tetrahedron *13*, 48 (1961); Advan. Chem. Phys. *4*, 67 (1962).

[58] *M. B. Groen, G. Stulen, G. J. Visser*, and *H. Wynberg*, J. Amer. Chem. Soc. *92*, 7218 (1970).

[59] *M. B. Groen*, Ph. D. dissertation, Groningen 1970; cf. also [75].

[60] *H. J. Bestmann* and *W. Both*, Angew. Chem. *84*, 293 (1972); Angew. Chem. int. Edit. *11*, 296 (1972).

[61] *H. J. Bestmann, R. Armsen*, and *H. Wagner*, Chem. Ber. *102*, 2259 (1969).

[62] *J. Tribout, R. H. Martin, M. Doyle*, and *H. Wynberg*, Tetrahedron Lett. *1972*, 2839.

[63] *J. A. Le Bel*, Bull. Soc. Chim. Fr. *22*, 347 (1874).

[64] *P. Boldt* and *W. Thielecke*, Chem. Ber. *104*, 353 (1971).

[65] a) *G. Tsoucaris, G. Balavoine, A. Moradpour, J. F. Nicoud*, and *H. Kagan*, C. R. Acad. Sci. *B 272*, 1271 (1971); b) *H. Kagan, A. Moradpour, J. F. Nicoud, G. Balavoine, R. H. Martin*, and *J. P. Cosyn*, Tetrahedron Lett. *1971*, 2479.

[66] *W. J. Bernstein, M. Calvin*, and *O. Buchardt*, J. Amer. Chem. Soc. *94*, 494 (1972).

[67] a) *W. J. Bernstein, M. Calvin*, and *O. Buchardt*, Tetrahedron Lett. *1972*, 2195; b) *W. J. Bernstein, M. Calvin*, and *O. Buchardt*, J. Amer. Chem. Soc. *95*, 527 (1973); cf. also *O. Buchardt*, Angew. Chem. *86*, 222 (1974); Angew. Chem. internat. Edit. *13*, 179 (1974).

[68] *R. H. Martin* and *M. J. Marchant*, Tetrahedron Lett. *1972*, 3707.

[69] *R. H. Martin* and *M. J. Marchant*, Tetrahedron *30*, 347 (1974).

[70] *Ch. Goedicke* and *H. Stegemeyer*, Tetrahedron Lett. *1970*, 937.

[71] *H. Wynberg* and *M. B. Groen*, Chem. Commun. *1969*, 964.

[72] *W. H. Laarhoven* and *R. G. M. Veldhuis*, Tetrahedron *28*, 1823 (1972).

[73] *R. C. Dougherty*, J. Amer. Chem. Soc. *90*, 5788 (1968).

[74] *M. S. Newman, R. S. Darlak*, and *L. Tsai*, J. Amer. Chem. Soc. *89*, 6191 (1967).

[75] *M. B. Groen* and *H. Wynberg*, J. Amer. Chem. Soc. *93*, 2968 (1971).

[76] *O. E. Weigang Jr.* and *P. A. Trouard-Dodson*, J. Chem. Phys. *49*, 4248 (1968).

[77] *R. H. Martin, N. Defay, H. P. Figeys, M. Flammang-Barbieux, J. P. Cosyn, M. Gelbcke*, and *J. J. Schurter*, Tetrahedron *25*, 4985 (1969).

[78] *C. W. Haig* and *R. B. Mallion*, Mol. Phys. *22*, 945, 955 (1971).

[79] *N. Defay*, Org. Magn. Resonance *6*, 221 (1974).

[80] *W. H. Laarhoven* and *R. J. F. Nivard*, Tetrahedron *28*, 1803 (1972).

[81] *N. Defay, D. Zimmerman*, and *R. H. Martin*, Tetrahedron Lett. *1971*, 1871.

[82] *R. H. Martin, J. Moriau*, and *N. Defay*, Tetrahedron *30*, 179 (1974).

[83] a) *H. Gunther*, Angew. Chem. *85*, 261 (1973); Angew. Chem. internat. Edit. *12*, 243 (1973); b) *R. H. Levin* and *J. D. Roberts*, Tetrahedron Lett. *1973*, 135.

[84] Cf. Ref. [59], p. 71.

[85] *M. J. Bishop* and *I. Fleming*, J. Chem. Soc. *C 1969*, 1712.

[86] a) *J. H. Dopper* and *H. Wynberg*, Tetrahedron Lett. *1972*, 763; b) *J. H. Dopper, D. Oudman*, and *H. Wynberg*, J. Amer. Chem. Soc. *95*, 3692 (1973).

[87] *W. Rhodes* and *M. F. A. El-Sayed*, J. Mol. Spectrosc. *9*, 42 (1962).

[88] *R. Chang* and *S. I. Weissman*, J. Amer. Chem. Soc. *89*, 5968 (1967).

[89] *R. Chang* and *S. I. Weissman*, J. Amer. Chem. Soc. *94*, 8683 (1972).

[90] *J. Klueger, G. Fischer, E. Fischer, Ch. Goedicke*, and *H. Stegemeyer*, Chem. Phys. Lett. *8*, 279 (1971).

[91] *E. Vander Donckt, J. Nasielski, J. R. Greenleaf*, and *J. B. Birks*, Chem. Phys. Lett. *2*, 409 (1968).

COMMUNICATIONS

Synthesis of the Active Derivative of Bovine Trypsin-Kallikrein Inhibitor (Kunitz) with Open Peptide Bond in the Reactive Site[**]

By *Helmut Jering* and *Harald Tschesche*[*]

Trypsin-kallikrein inhibitors (type Kunitz)[2, 3] occupy a special place among the natural, low molecular weight proteinase inhibitors I[1, 2]. As a rule, inhibitors suffer partial proteolysis during substrate analogous attachment to the enzyme; the peptide bond $-P_1-P_1'-$ in the reactive site[1, 2] is opened and modified inhibitors I* still possessing full inhibitory activity are formed. So far, this modification could not be established in the case of Kunitz type trypsin-kallikrein inhibitors[1, 2, 4].

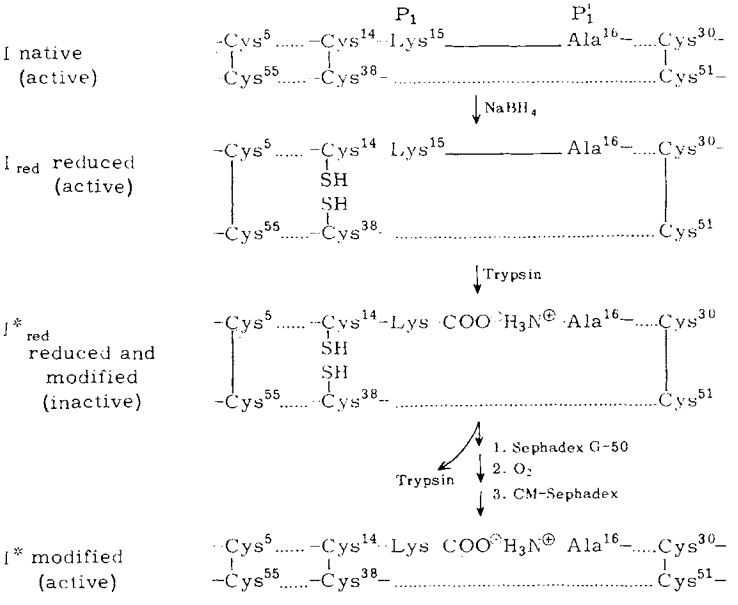
We have now succeeded in preparing the modified form I* of an inhibitor of the Kunitz type. The initial step involved selective reduction of one of the three disulfide bridges, the Cys 14—Cys 38 disulfide bridge adjacent to the reactive site, with $NaBH_4$ in aqueous solution[5]. The selectively reduced inhibitor is degraded by trypsin by successive cleavages of the Lys 15—Ala 16, Arg 39—Ala 40 and Arg 17—Ile 18 bonds, the first cleavage of which leads to deactivation of the inhibitor[5]. In order to ensure that cleavage is restricted to the Lys 15—Ala 16 bond, selectively reduced inhibitor was incubated with 20 mol-% trypsin at pH = 3.7 with exclusion of oxygen (to avoid reoxidation of the disulfide bridge Cys 14—Cys 38) just until excess inhibitor was inactivated. Finally, the trypsin was separated from the inhibitor by gel filtration on Sephadex G-50 and the disulfide bridge Cys 14—Cys 38 reoxidized again with O_2 at pH = 8.6 (0.1 M Na-borate). Purification of this modified inhibitor was accomplished by ion-exchange chromatography on CM-Sephadex with a NaCl gradient at pH = 8.6 (see Scheme 1).

The structure of the modified bovine inhibitor I* (Kunitz) can be deduced from the following data[6]: a) same amino acid composition as the starting material I; b) one uniform band on disc electrophoresis at pH = 9.3—because of the additional negative charge I migrates slower (70 % of the migrating distance) than I; c) performic acid oxidation and isolation of the two polypeptide chains that are formed (amino acid residues 1—15 and 16—58); d) complete inactivation of I* by cleavage of Lys 15 with 0.03 mol-% carboxypeptidase B within one hour at room temperature; e) enzymatically catalyzed resynthesis of the peptide bond Lys 15—Ala 16 with regeneration of starting material I[7].

The modified inhibitor I* inhibits the enzymes trypsin and chymotrypsin (from beef), the same complex being formed from enzyme and modified inhibitor as from enzyme and native (unmodified) inhibitor[8]. However, the ratios of the rate constants for complex formation with native (k) or with

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Scheme 1

modified (k^*) inhibitor are different for α-chymotrypsin ($k/k^* = 2.2 \times 10^4$) and β-trypsin ($k/k^* = 50$)[8].

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[1] *M. Laskowski, Jr.* and *R. W. Sealock* in *P. D. Boyer*: The Enzymes. Vol. III, Academic Press, New York 1971, p. 375.

[2] *H. Tschesche*, Angew. Chem. *86*, 21 (1974); Angew. Chem. internat. Edit. *13*, 10 (1974).

[3] *B. Kassel* and *M. Laskowski, Sr.*, Biochem. Biophys. Res. Commun. *20*, 463 (1965).

[4] *H. Tschesche* and *R. Obermeier* in *H. Fritz* and *H. Tschesche*: Proceedings of the International Research Conference on Proteinase Inhibitors, de Gruyter, Berlin 1971, p. 135.

[5] *L. F. Kress* and *M. Laskowski, Sr.*, J. Biol. Chem. *242*, 4925 (1967). *L. F. Kress, K. A. Wilson*, and *M. Laskowski, Sr., ibid. 246*, 3555 (1971). *W. K. Liu* and *J. Meienhofer*, Biochem. Biophys. Res. Commun. *31*, 467 (1968).

[6] *H. Tschesche, H. Jering, G. Schorp*, and *T. Dietl* in *H. Fritz, H. Tschesche, L. J. Greene*, and *E. Truscheit*: Proteinase Inhibitors, 2nd International Research Conference—Bayer Symposium V. Springer, Berlin, in press.

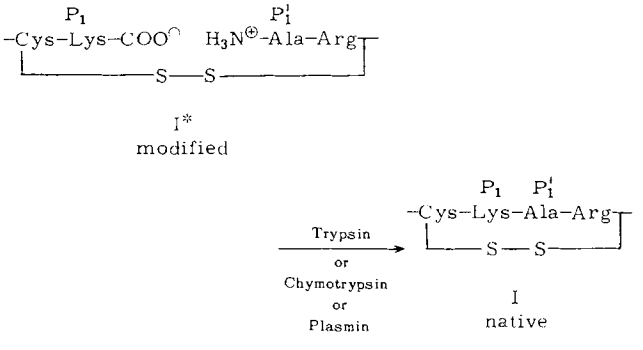
[7] *H. Jering* and *H. Tschesche*, Angew. Chem. *86*, 703 (1974); Angew. Chem. internat. Edit. *13*, 661 (1974).

[8] *U. Quast, J. Engel, E. Steffen, G. Mair, H. Tschesche*, and *H. Jering*, Eur. J. Biochem., in press.

Proteinase Catalyzed Resynthesis of the Peptide Bond Lys 15—Ala 16 in the Derivative of Trypsin-Kallikrein Inhibitor (Kunitz) with this Peptide Bond Hydrolyzed[**]

By *Helmut Jering* and *Harald Tschesche*[*]

The open —P_1—P_1'— bond (Lys 15, Ala 16)[1] in modified trypsin-kallikrein inhibitor I* (Kunitz) from bovine organs can be resynthesized with trypsin, chymotrypsin and plasmin. The long reaction times (half-lives corresponding to 17 weeks[2]) due to slow dissociation of the enzyme-inhibitor-complex were shortened by employing equimolar amounts of trypsin (porcine) or chymotrypsin (bovine) at pH = 7.8 (0.2 M tris(2-hydroxyethyl)ammonium chloride/NaOH, 0.01 M $CaCl_2$) and room temp. The complexes were dissociated after 1 h (trypsin) and 48 h (chymotrypsin), respectively, at pH = 1.7 and the enzyme and inhibitor were then separated on Sephadex G-50 at the same pH. In both cases the sole products isolated were the enzyme and the native inhibitor I with intact peptide bond —P_1—P_1'— (kinetically controlled dissociation[3]). A complete resynthesis could also be achieved with catalytic amounts (20 mol-%) of β-trypsin (bovine) at room temperature and pH = 3.7 within 24 h (thermodynamically controlled resynthesis).



The structure of the inhibitor with resynthesized peptide bond was apparent from the following data, which were in accord with those for the native inhibitor: a) amino acid composition; b) migration of the homogeneous inhibitor on disc electrophoresis at pH = 9.3; c) performic acid oxidation yields only one polypeptide chain (amino acids 1–58); d) kinetic constants of the complex formation with enzyme (inhibition curve)[4]; e) difference spectra of the complexes of enzyme with I and I*[4]; f) resistance to inactivation with carboxypeptidase B (2 mol-% in 0.025 M Tris-HCl buffer, pH = 7.2, 24 h at 25 °C). The resynthesis shows that the equilibrium of the enzymatically catalyzed proteolysis of the peptide bond —P_1—P_1'— lies completely on the side of the native inhibitor. This explains the

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failure of attempts to prepare the modified inhibitor by direct partial proteolysis of the native protein. Furthermore, the resynthesis of the peptide bond Lys 15—Ala 16 with catalytic amounts of trypsin, chymotrypsin or plasmin proves that the reactive site of the inhibitor for these three enzymes is the same. Thus the trypsin-kallikrein inhibitor (Kunitz) is to be classified as single-headed[5, 6].

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[1] *H. Jering* and *H. Tschesche*, Angew. Chem. *86*, 702 (1974); Angew. Chem. internat. Edit. *13*, 660 (1974).

[2] *J. P. Vincent* and *M. Lazdunski*, Biochemistry *11*, 2967 (1972).

[3] *W. R. Finkenstadt* and *M. Laskowski, Jr.*, J. Biol. Chem. *242*, 771 (1967).

[4] *U. Quast, J. Engel, E. Steffen, G. Mair, H. Tschesche*, and *H. Jering*, Eur. J. Biochem., in press.

[5] *M. Laskowski, Jr.* and *R. W. Sealock* in *P. D. Boyer*: The Enzymes. Vol. III, Academic Press, New York 1971, p. 375.

[6] *H. Tschesche*, Angew. Chem. *86*, 21 (1974); Angew. Chem. internat. Edit. *13*, 10 (1974).

Replacement of Lysine by Arginine, Phenylalanine, and Tryptophan in the Reactive Site of the Trypsin-Kallikrein Inhibitor (Kunitz)[**]

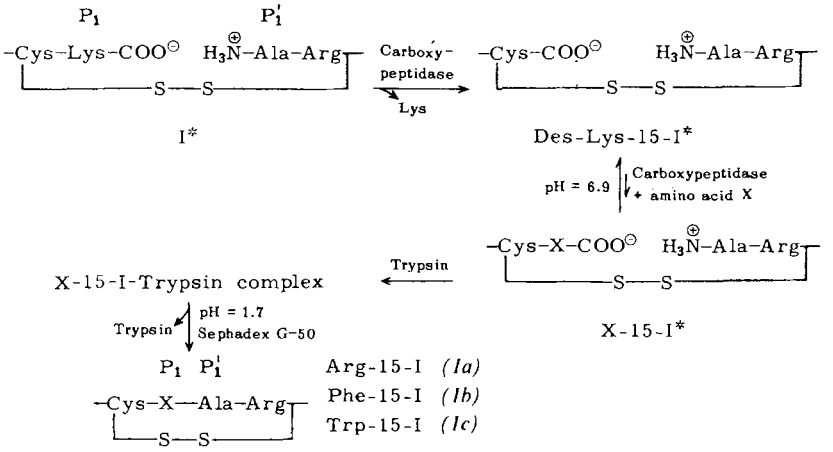
By *Helmut Jering* and *Harald Tschesche*[*]

Cleavage of the P_1 residue from the reactive site of modified proteinase inhibitors I* with carboxypeptidase B inactivates the inhibitors[1]. The cleavage is accompanied by a reduction in the association constant K_{ass} (formation of enzyme-inhibitor complex) of about five to ten orders of magnitude. Reinsertion of a proteinase (*e.g.* trypsin) the high association constant for complex formation ($K_{ass} \approx 10^{10}$—10^{14} mol/l) can be utilized for displacing the equilibrium of the carboxypeptidase-catalyzed reaction, *i.e.* for reincorporation of the residue P_1[2, 3].

We have now used this reaction for insertion of arginine in position 15 of the modified trypsin-kallikrein inhibitor I* (Kunitz)[4] after cleavage of the Lys-15 residue [50 mg I*, 20 units of carboxypeptidase B (Merck) in 1 ml 0.025 M Tris/HCl, pH = 7.2, 0.1 M NaCl, 16 h at room temperature]. The modified des-Lys-15 inhibitor can be isolated by ion-exchange chromatography. It exhibits a single band in the disc electrophoresis and due to a lack of one positive charge it migrates at a slower rate than I*. According to amino acid analysis it contains exactly one lysine less than I*, and when subjected to the usual tests[5] proves to be inactive toward trypsin.

Incorporation of arginine was accomplished by dissolving 1.23 µmol des-Lys-15 inhibitor, 2.46 µmol trypsin (porcine) and 0.02 µmol carboxypeptidase B (Merck) in 2.4 ml buffer (0.1 M tris(2-hydroxyethyl)ammonium chloride/NaOH, 0.15 M KCl, 0.03 M $CaCl_2$ and 0.01 M NaN_3) at pH = 6.9 and incubating the resulting solution with 0.6 ml 0.25 M L-arginine in the same buffer for six days at room temperature. The resulting trypsin-inhibitor complex was then acidified to pH = 1.7 and separated into enzyme and inhibitor fractions by molecular sieve filtration on Sephadex G-50. Ion-exchange on CM-Sephadex C-25 afforded 0.25 µmol unmodified Arg-15-trypsin-kallikrein inhibitor (Kunitz) (Scheme 1).

The Arg-15 inhibitor *(1a)* obtained by enzymatic replacement is characterized by the following data: a) amino acid composition; uniformly migrating band on disc electrophoresis; c) complete resistance to inactivation by carboxypeptidase B (2 mol-% for two days), and d) the same inhibitory activity



Scheme 1. For Arg-insertion with trypsin, carboxypeptidase B was used; for Phe- and Trp-insertion with chymotrypsin, carboxypeptidase A was used. (a), X = Arg; (b), X = Phe; (c), X = Trp.

of the residue P_1, *e.g.* in the reverse reaction of the carboxypeptidase cleavage in the presence of a large excess of free amino acid P_1, increases K_{ass} by the same amount. In the presence of a proteinase (*e.g.* trypsin) the high association constant for complex formation ($K_{ass} \approx 10^{10}$—10^{14} mol/l) can be utilized for displacing the equilibrium of the carboxypeptidase-catalyzed reaction, *i.e.* for reincorporation of the residue P_1[2, 3].

We have now used this reaction for insertion of arginine in position 15 of the modified trypsin-kallikrein inhibitor I* (Kunitz)[4] after cleavage of the Lys-15 residue [50 mg I*, 20 units of carboxypeptidase B (Merck) in 1 ml 0.025 M Tris/HCl, pH = 7.2, 0.1 M NaCl, 16 h at room temperature]. The modified des-Lys-15 inhibitor can be isolated by ion-exchange chromatography. It exhibits a single band in the disc electrophoresis and due to a lack of one positive charge it migrates at a slower rate than I*. According to amino acid analysis it contains exactly one lysine less than I*, and when subjected to the usual tests[5] proves to be inactive toward trypsin.

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The Arg-15 inhibitor *(1a)* obtained by enzymatic replacement is characterized by the following data: a) amino acid composition; uniformly migrating band on disc electrophoresis; c) complete resistance to inactivation by carboxypeptidase B (2 mol-% for two days), and d) the same inhibitory activity towards the enzymes trypsin, chymotrypsin and plasmin as the native lysine inhibitor. Whether differences exist in the rate constants of association to the enzyme-inhibitor complex between native and Arg-15 inhibitor is at present under investigation. In an analogous reaction sequence with carboxypeptidase A and chymotrypsin under corresponding conditions we have been able to incorporate the amino acids phenylalanine and tryptophan as residue P_1. In contrast to the inhibitors with Lys or Arg in the reactive site, the homologous Phe and Trp-inhibitors *(1b)* and *(1c)* are poor trypsin but good chymotrypsin inhibitors. Corresponding results were obtained with the soybean inhibitor (Kunitz)[2, 3].

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The Arg-15 inhibitor contains a single-stranded peptide chain and thus corresponds to a protein with the mutation Lys 15 →Arg 15. We have also found this substitution as a natural mutation in the homologous isoinhibitors from snails *(Helix pomatia)*[6].

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[1] *W. R. Finkenstadt* and *M. Laskowski, Jr.*, J. Biol. Chem. *240*, PC 962 (1965); *M. Laskowski, Jr.* and *R. W. Sealock* in *P. D. Boyer*: The Enzymes. Vol. III, Academic Press, New York 1971, p. 375.

[2] *R. W. Sealock* and *M. Laskowski, Jr.*, Biochemistry *8*, 3703 (1969).

[3] *T. R. Leary* and *M. Laskowski, Jr.*, Federat. Proc. (1973); *D. Kowalski, T. R. Leary, R. E. McKee, R. W. Sealock, D. Wang*, and *M. Laskowski, Jr.* in *H. Fritz, H. Tschesche, L. J. Greene*, and *E. Truscheit*: Proteinase Inhibitors, 2nd International Research Conference—Bayer Symposium V. Springer, Berlin, in press.

[4] *H. Jering* and *H. Tschesche*, Angew. Chem. *86*, 702 (1974); Angew. Chem. internat. Edit. *13*, 660 (1974).

[5] *H. Fritz, I. Trautschold*, and *E. Werle* in *H. U. Bergmeyer*: Methoden der enzymatischen Analyse. Verlag Chemie, Weinheim 1970. 2. Edit., Vol. 1, p. 1011 ff.

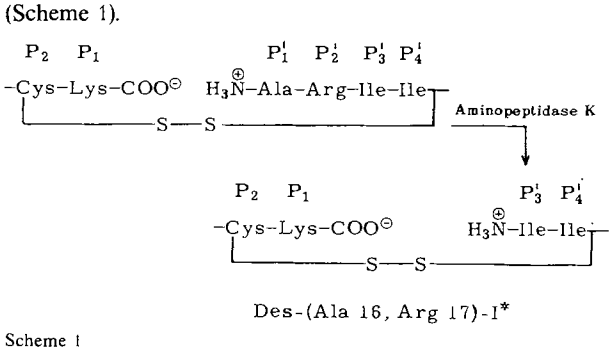
[6] *H. Tschesche* and *T. Dietl*, Eur. J. Biochem. *30*, 560 (1972); *T. Dietl* and *H. Tschesche* in [3].

Inactivation of the Trypsin-Kallikrein Inhibitor (Kunitz) by Cleavage of the Dipeptide Ala 16—Arg 17 in the Reactive Site[**]

By *Helmut Jering* and *Harald Tschesche*[*]

Cleavage of the residue P_1 (Lys 15) from the reactive site of the modified trypsin-kallikrein inhibitor I* (Kunitz)[1] inactivates the inhibitor[2]. The question arises, whether removal of the residue P_1' (Ala 16) likewise inactivates the inhibitor, even though the formation of an acyl-enzyme complex at P_1 is still possible as an intermediate step enroute to the stable enzyme-inhibitor complex C[3].

Cleavage of the residue P_1' (Ala 16) from I* meets with difficulties, since Edman degradation as used for soybean trypsin inhibitor (Kunitz)[4] is not applicable owing to inactivation of the inhibitor (N^{ε}-derivatization), and several aminopeptidases [leucine aminopeptidase from bovine eye lenses (M.W. 300000[5]), aminopeptidase M, *etc.*] do not attack I*. Because of its small molecular weight (19000[6]) aminopeptidase K is effective and cleaves the residues P_1' and P_2' (Ala 16 and Arg 17) within 20 minutes (0.5 µmol I*, 0.2 mol-% aminopeptidase K in 1.5 ml 0.025 M diethyl barbiturate buffer, pH = 8.3) (Scheme 1).



Scheme 1

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The reaction can be so steered that up to 95% modified des-(Ala 16, Arg 17)-inhibitor is formed. Prolonged enzyme reaction cleaves also Ile 18.—The reaction then comes to a standstill.

The modified des-(Ala 16, Arg 17)-inhibitor could be separated from the enzyme by molecular sieve filtration on Sephadex G-50 in 0.1 M acetic acid and was purified by ion-exchange chromatography on CM-Sephadex C-25 in 0.01 M sodium borate buffer, pH = 8.0 (linear NaCl gradient of 0 to 0.3 M). The homogeneous material is characterized by its amino acid composition. Native inhibitor is not attacked at the *N*-terminus (Arg-Pro-Asp-Phe-) by aminopeptidase K.

After cleavage of the residues P_1' and P_2', I* is inactive towards trypsin in the usual test[7], *i.e.* the association constant K_{ass} is reduced by about 8 to 10 orders of magnitude. Whether the acyl-enzyme complex still forms as an intermediate is at present under investigation. Since Arg 17 contributes substantially to the stabilization of the complex[3] a drastic reduction in the association constant K_{ass} had to be reckoned with; however, according to X-ray structural data for the crystallized complex[3] there should still be sufficient interaction for oriented incorporation of des-(Ala 16, Arg 17)-inhibitor into the enzyme.

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[1] *H. Jering* and *H. Tschesche*, Angew. Chem. *86*, 702 (1974); Angew. Chem. internat. Edit. *13*, 660 (1974).

[2] *H. Jering* and *H. Tschesche*, Angew. Chem. *86*, 703 (1974); Angew. Chem. internat. Edit. *13*, 661 (1974).

[3] *R. Huber, D. Kukla, W. Steigemann, J. Deisenhofer*, and *A. Jones* in *H. Fritz, H. Tschesche, L. J. Greene*, and *E. Truscheit*: Proteinase Inhibitors, 2nd International Research Conference—Bayer Symposium V. Springer, Berlin, in press; see also *H. Tschesche*, Angew. Chem. *86*, 21 (1974); Angew. Chem. internat. Edit. *13*, 10 (1974).

[4] *D. Kowalski, T. R. Leary, R. E. McKee, R. W. Sealock, D. Wang*, and *M. Laskowski, Jr.* in *H. Fritz, H. Tschesche, L. J. Greene*, and *E. Truscheit*: Proteinase Inhibitors, 2nd International Research Conference—Bayer Symposium V. Springer, Berlin, in press.

[5] *S. R. Himmelhoch* and *E. A. Peterson*, Biochemistry 7, 2085 (1968).

[6] *N. Hennrich, M. Klockow, H. D. Orth, U. Femfert, P. Cichocki*, and *K. Jany*, Hoppe-Seylers Z. Physiol. Chem. *354*, 1339 (1973).

[7] *H. Fritz, I. Trautschold*, and *E. Werle* in *H. U. Bergmeyer*: Methoden der enzymatischen Analyse, Verlag Chemie, Weinheim 1970. 2. Edit., Vol. 1, p. 1011 ff.

Photoisomerization of Tricyclo[5.2.1.$0^{4,10}$]deca-2,5,8-triene (Triquinacene)[**]

By *Dieter Bosse* and *Armin de Meijere*[*]

Thermal isomerization of diademane *(1)*[1] leads to triquinacene *(2)*. The reverse reaction is, however, conceivable only as a photochemical two-step process. Because of the di-π-methane system present in the molecule *(2)*[2] a diradical of structure *(3)* should be formed as the first intermediate upon excitation by light. There then arises the interesting question whether an intramolecular cycloaddition of *(3)* to yield *(1)* can occur.

With this in view we irradiated a 0.8 percent pentane solution of *(2)* in a falling-film recycling apparatus at −40°C by

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means of a 150-watt Hg medium-pressure lamp (Hanau TQ 150, quartz immersion well). *Ca.* 40—45% of the starting material had reacted after 30—50 h. At least eight new com-



(1) *(2)* *(3)*

ponents could be detected, along with polymeric material, by gas chromatography of the reaction mixture. So far seven of these products have been identified.

First there were the three known $(CH)_{10}$ isomers: bicyclo[4.2.2]decatetraene *(4)* (relative proportion 9%), tricyclo[4.2.2.$0^{2,5}$]deca-3,7,9-triene *(5)* (6%), and bullvalene *(6)* (5%), as well as naphthalene *(7)* (3%) and azulene *(8)* (trace). According to mass-spectrometric molecular weight determinations the two main products were also isomers of molecular formula $C_{10}H_{10}$; on the basis of their spectroscopic and chemical behavior the hitherto unknown structures pentacyclo[4.4.0.0.^{2,4}.$0^{3,10}$.$0^{5,9}$]dec-7-ene *(9)*[3] and hexacyclo-[4.4.0.$0^{2,4}$.$0^{3,10}$.$0^{5,8}$.$0^{7,9}$]decane *(10)*[4] were assigned to them (see Table 1).

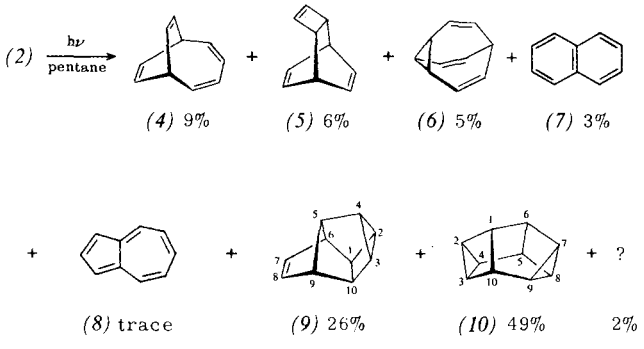


Table 1. NMR spectra of *(9)* and *(10)* [a].

Cpd.	^{1}H-NMR (τ) in CCl_4	^{13}C-NMR (δ) [b] [5]
(9)	4.56 (A_2 part of an A_2X_2 system, H^7, H^8) 7.11 (m, H^5) 7.22 (m, H^6, H^9) 7.84 (dt, H^2, H^3) 7.99 (m, H^1, H^{10}) 8.79 (m, H^4)	
(10)	7.13 (m, H^1, H^6, H^5, H^{10}) 8.11 (m, H^3, H^8) 8.47 (m, H^2, H^7) 9.03 (m, H^4, H^9)	14.39 (d, C^3, C^8; $J_{^{13}C^3-H^3}$ = 179 Hz) 19.10 (d, C^4, C^9; $J_{^{13}C^4-H^4}$ = 163 Hz) 22.24 (d, C^2, C^7; $J_{^{13}C^2-H^2}$ = 183 Hz) 36.83 (d, C^5, C^{10}; $J_{^{13}C^5-H^5}$ = 143 Hz) 52.66 (d, C^1, C^6; $J_{^{13}C^1-H^1}$ = 149 Hz)

[a] The assignment was confirmed by double resonance experiments.
[b] Relative to tetramethylsilane.

Although crystalline *(10)* (m.p. 42 °C) is a highly strained molecule since it contains two bicyclopentyl units, it is nevertheless relatively stable thermally: no rearrangement could be detected after heating a toluene solution for 5 h at 200 °C.

Upon catalytic hydrogenation (10% Pd/C) *(10)* readily took up two moles of hydrogen yielding the known tetracyclo[5.2.1.$0^{2,6}$.$0^{4,8}$]decane (m.p. 158 °C), which was identified by comparison of its characteristic NMR spectrum with that of an authentic sample[6].

Diademane *(1)* is definitely not formed on photolysis of *(2)*. When *(9)* and *(10)* are included, 23 of the 91 theoretically possible $(CH)_{10}$ isomers[7] are now known.

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CAS Registry Numbers:
(2): 6053-74-3 / *(9)*: 52674-18-7 / *(10)*: 52674-19-8.

[1] *A. de Meijere, D. Kaufmann,* and *O. Schallner,* Angew. Chem. *83*, 404 (1971); Angew. Chem. internat. Edit. *10*, 417 (1971).

[2] *S. S. Hixson, P. S. Mariano,* and *H. E. Zimmermann,* Chem. Ber. *73*, 531 (1973).

[3] *E. L. Allred* (personal communication) and *L. A. Paquette* (cf. *M. J. Wyvratt* and *L. A. Paquette,* Tetrahedron Lett. *1974*, 2433) have recently obtained the $(CH)_{10}$ hydrocarbon *(9)* independently by different routes.

[4] In accord with a proposal by Prof. *W. Walter,* Hamburg, we name this new $(CH)_{10}$ hydrocarbon "barettane" since its molecular shape is reminiscent of a baretta.

[5] The ^{13}C-NMR spectrum was measured by Dr. *S. Braun,* Darmstadt.

[6] Prepared by catalytic hydrogenation of pentacyclo[5.2.1.$0^{2,6}$.$0^{3,9}$.$0^{4,8}$]decane. *J. E. Baldwin* (Eugene, Oregon, USA), personal communication.

[7] *A. T. Balaban,* Rev. Roum. Chim. *11*, 1097 (1966); *17*, 865 (1972); *A. L. Allred* and *B. R. Beck,* J. Amer. Chem. Soc. *95*, 2393 (1973).

Modified Horeau Analysis for Determination of the Chirality of Amines, Alcohols, and Carboxylic Acids[**]

By *Hans Brockmann Jr.* and *Nikolaus Risch*[*]

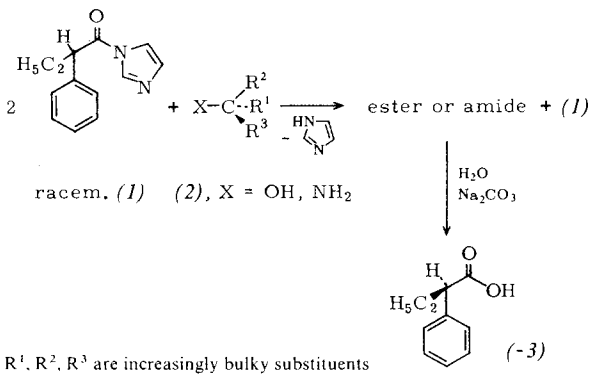
Stereospecific reactions can be applied for correlation of configurations of chiral compounds if their course can be predicted on the basis of empirical rules or theoretical considerations. If the absolute configuration of one reactant is known, the chirality of a second can then be derived. Two procedures based on this principle have proved of value for determination of the configuration of secondary alcohols: the asymmetrically induced synthesis of atrolactic esters[1], which can be described by *Ruch* and *Ugi*'s stereochemical analogy model[2], and the method of partial kinetic resolution of bis-(2-phenylbutyric) anhydride developed by *Horeau*[3,4]. Unfortunately Horeau analyses cannot be applied to determine the configuration of amines[5].

We replaced bis-(2-phenylbutyric) anhydride by 1-(2-phenylbutyroyl)imidazole *(1)*, which is easily accessible from 2-phenylbutyric acid and *N,N'*-carbonyldiimidazole, and we then found (Table 1) that its alcoholysis and aminolysis in benzene or THF as solvent occurred with equal stereoselectivity. Although the new procedure—which can be carried out with pure *(1)* or in a single vessel without intermediate isolation—requires longer reaction times for determination of the chirality of alcohols and gives somewhat lower optical yields than the conventional Horeau analysis, the stereoselectivity in aminolyses of *(1)* is generally higher than in aminolyses of bis-(2-phenylbutyric) anhydride (the optical yield in expt. No. 6 of Table 1 amounts to 14 to 36% depending on the reaction temperature[6]).

(1) can be easily prepared in high enantiomeric purity from optically active 2-phenylbutyric acid and then used for partial resolution of racemic alcohols and amides. If *(-1)* is used for this purpose, the chirality *(2a)* of the residual excess of compound *(2)* can be predicted.

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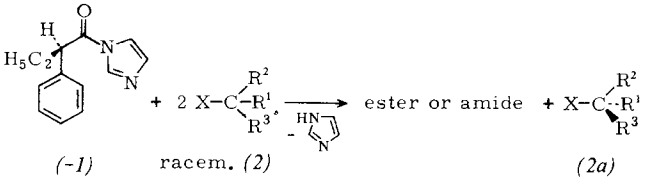
racem. *(1)* *(2)*, X = OH, NH_2

R^1, R^2, R^3 are increasingly bulky substituents

Table 1. Experiments for determination of the absolute configuration of alcohols and amines. Experiments Nos. 1—3, 6 and 7 were carried out also with the enantiomers.

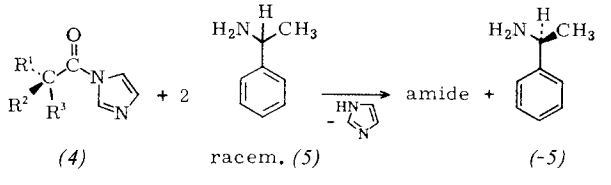
No.	Cpd. studied *(2)*	Sign of optical rotn. of *(3)*	Abs. confign. Found	Lit.
1	(+)-α-Methylbenzyl alcohol	+	*R*	*R*
2	(+)-1-(1-Naphthyl)ethanol	+	*R*	*R*
3	(−)-Pinacolyl alcohol	+	*R*	*R*
4	(−)-Menthol	+	*R*	*R*
5	(+)-Testosterone	−	*S*	*S*
6	(+)-α-Methylbenzylamine	+	*R*	*R*
7	(+)-1-(1-Naphthyl)ethylamine	+	*R*	*R*
8	L-Alanine ethyl ester	−	*S* [a]	*S*
9	L-Leucine methyl ester	−	*S* [a]	*S*
10	L-Tryptophan methyl ester	+	*S* [a]	*S*

[a] It is assumed that the ethoxycarbonyl and methoxycarbonyl groups are bulkier than CH_3 or $(CH_3)_2CHCH_2$, but less bulky than the indole group of tryptophan.



(-1) racem. *(2)* *(2a)*

Finally, the imidazole procedure permits determination of the configuration of chiral carboxylic acids: thus if an excess of racemic *(5)* is allowed to act on an optically active 1-acylimidazole *(4)*, the sign of the optical rotation of the residual amine can be used to decide the configuration of the carboxylic acid used, as shown in the formulas (cf. Table 2).



(4) racem. *(5)* *(-5)*

Table 2. Experiments for determination of the absolute configuration of carboxylic acids by way of their imidazolides *(4)*.

No.	Acid studied	Sign. of opt. rotn. of *(5)*	Abs. confign. Found	Lit.
1	(−)-2-Phenylbutyric	−	*R*	*R*
2	(−)-Hydratropic	−	*R*	*R*
3	(+)-*O*-Acetylmandelic	+	*R*	*R*
4	(−)-2-(9-Carbazolyl)propionic	−	*S*	?

Although the reagent *(1)* used by us and also the imidazolides *(4)* of the carboxylic acids listed in Table 2 belong to chirality class A[2], a description of the reaction course by *Ruch* and *Ugi*'s stereochemical analogy model[2] seems to us to meet as many problems as that of conventional Horeau analyses, since the two diastereoisomeric products can be formed through more than two corresponding transition complexes.

Experimental:

The acid *(3)* (328 mg, 2 mmol) is added to a suspension of 1,1'-carbonyldiimidazole (324 mg, 2 mmol) in anhydrous benzene (4 ml) and the mixture is stirred at 22 °C until evolution of CO_2 ceases. Then the base *(+5)* (121 mg, 1 mmol) in anhydrous benzene (1 ml) is added dropwise and the reaction mixture is left for 15 h at 22 °C. The mixture is then separated by repeated shaking between benzene (20 ml) and 10% aqueous NaOH solution (20 ml), the aqueous phase is washed again with benzene, acidified with 5 N HCl, and the *(3)* precipitated is extracted in benzene. Evaporation of this solution after it had been washed twice with water and dried over Na_2SO_4 yielded 140 mg of *(3)*, $[\alpha]_{578}^{22} = 13.4°$ in benzene. Chromatography of the benzene phase on silica gel affords the mixture of diastereoisomeric amides, whose isomer proportions were found by ^{1}H-NMR spectrometry to be 57:43.

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CAS Registry Numbers:
(±)-*(1)*: 52699-46-4 / (−)-2-(*N*-carbazolyl)propionic acid: 52730-59-3.

[1] *V. Prelog*, Bull. Soc. Chim. Fr. *1956*, 987.
[2] *E. Ruch* and *I. Ugi*, Top. Stereochem. *4*, 99 (1969).
[3] *A. Horeau*, Tetrahedron Lett. *1961*, 506; *1962*, 965.
[4] *A. Horeau* and *H. Kagan*, Tetrahedron *20*, 2431 (1964).
[5] *H. Brockmann jr.* and *J. Bode*, Liebigs Ann. Chem. *748*, 20 (1971).
[6] Lowering the reaction temperature lowers the reaction rate but increases the stereoselectivity. The optical yield of 36% is achieved at −22 °C.

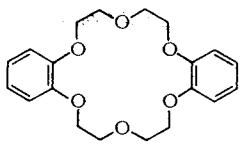
Crown Ethers as Catalysts in Reactions of Carbanions and Halocarbenes[1]

By *M. Mąkosza* and *M. Ludwikow*[*]

Catalytic reactions of carbanions and halocarbenes in two-phase liquid systems have become important and versatile tools in organic synthesis in recent years. Suitable catalysts for these reactions are quaternary ammonium[2,3] and phosphonium compounds[4]. The decisive reaction step is the formation of ion-pairs of the type $>\overset{\oplus}{N}<A^{\ominus}$ (where $A^{\ominus}$ = carbanion), which are soluble in the organic phase where they undergo further transformations with simultaneous liberation of the quaternary ammonium ions[5]. The organic "onium" cations can be substituted to some extent in these reactions by inorganic cations ($Na^{\oplus}$ or $K^{\oplus}$) when the latter are strongly solvated or complexed.

Among the most powerful complexing agents for alkali metal ions are the crown ethers[6]. As we have found, many two-phase reactions of carbanions and halocarbenes can be effectively catalyzed by crown ethers, especially dibenzo[18]crown-6 *(1)*. Addition of only a small amount of *(1)* (1 mol-%) to a two-phase system consisting of C—H acid (with or without organic solvent) and concentrated aqueous NaOH solution results in formation of Na[crown ether]$^{\oplus}$ carbanion$^{\ominus}$ ion-pairs, which are soluble in the organic phase where they undergo further transformation.

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(1)

$$\text{>C-H} \xrightarrow[\text{NaOH}_{aq}]{(1)} \text{>C}^{\ominus}\ \text{Na}\ (1)^{\oplus}$$

We have studied: a) the alkylation of C—H acids, b) reactions involving trichloromethyl anion and dichlorocarbene, c) reactions of carbanions with aromatic nitro compounds, and d) Darzens condensations in systems containing *(1)*. The following are a few examples.

$$(H_5C_6)_2CH\text{-}CN + BrCH_2\text{-}CH_2Br \xrightarrow[\text{NaOH}_{aq}]{(1)} (H_5C_6)_2C(CN)\text{-}CH_2\text{-}CH_2Br$$

(2) *(3)*

$$CHCl_3 + H_5C_6\text{-}CH{=}CH_2 \xrightarrow[\text{NaOH}_{aq}]{(1)}$$

(4)

(5) $p\text{-}NO_2\text{-}C_6H_4\text{-}C(C_6H_5)(CH_3)\text{-}CN$ $\qquad$ H_5C_6-substituted epoxide *(6)*

a) Addition of 1 mol-% of *(1)* to a stirred mixture of phenylacetonitrile or diphenylacetonitrile *(2)*, alkyl chloride or bromide and 50% aqueous NaOH results in an exothermic reaction. Phenylacetonitrile and ethyl bromide give 2-phenylbutyronitrile[2] (b. p. 120°C/15 torr, yield 85%); *(2)* and 1,2-dibromoethylene give 4-bromo-2,2-diphenylbutyronitrile *(3)*[2] (m. p. 69°C, yield 75%).

b) Mild exothermic reaction of chloroform, styrene, and 50% aqueous NaOH in the presence of 1 mol-% of *(1)* gave 1,1-dichloro-2-phenylcyclopropane *(4)* (b. p. 110°C/15 torr, yield 87%). High yields of dichlorocyclopropane derivatives have also been obtained with other alkenes. Acrylonitrile gave 4,4,4-trichlorobutyronitrile (m. p. 41°C, yield ca. 40%)[7].

c) Reaction of 2-phenylpropionitrile, 1-chloro-4-nitrobenzene and 50% aqueous NaOH in the presence of *(1)* gave 2-(4-nitrophenyl)-2-phenylpropionitrile *(5)* (conditions see Ref.[2b]) (m. p. 76°C, yield 81%). 4-Nitrobenzophenone is converted into 2-(4-benzoylphenyl)-2-phenylpropionitrile[2c] (m. p. 63°C, yield 67%).

d) Darzens condensation of benzaldehyde and chloroacetonitrile in aqueous NaOH in the presence of *(1)* gave 3-phenyloxirane-2-carbonitrile *(6)* as a mixture of isomers (b. p. 137 to 140°C/15 torr, yield 78%) (cf. Ref.[2d]).

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CAS Registry Numbers:
(1): 14187-32-7 / *(2)*: 86-29-5 / *(3)*: 39186-58-8 / *(4)*: 2415-80-7 / *(5)*: 22156-51-0 / *(6)*: 33863-75-1 / phenylacetonitrile: 140-29-4 / ethyl bromide: 74-96-4 / 1,2-dibromoethane: 106-93-4 / chloroform: 67-66-3 / styrene: 100-42-5 / dichlorocyclopropane: 2088-35-9 / acrylonitrile: 107-13-1 / 2-phenylpropionitrile: 1823-91-2 / 1-chloro-4-nitrobenzene: 100-00-5 / 4-nitrobenzophenone: 1144-74-7 / 2-(4-benzoylphenyl)-2-phenylpropionitrile: 33092-22-7 / 4,4,4-trichlorobutyronitrile: 19376-56-8.

[1] Reactions of Organic Anions, Part 54.—Part 53: Rocz. Chem., in press.

[2] a) *M. Mąkosza* and *B. Serafin*, Rocz. Chem. *39*, 1407, 1595 (1965); *40*, 1839 (1966); b) *M. Mąkosza*, Tetrahedron Lett. *1969*, 673; c) *M. Mąkosza* and *M. Ludwikow*, Bull. Acad. Pol. Sci., Ser. Sci. Chim. *19*, 231 (1971); d) *A. Jończyk*, *M. Fedoryński*, and *M. Mąkosza*, Tetrahedron Lett. *1972*, 2394.

[3] *M. Mąkosza* and *M. Wawrzyniewicz*, Tetrahedron Lett. *1969*, 4659.

[4] a) *C. Starks*, J. Amer. Chem. Soc. *93*, 175 (1971); b) *W. P. Weber* and *J. P. Shepherd*, Tetrahedron Lett. *1972*, 4907.

[5] *E. V. Dehmlow*, Angew. Chem. *86*, 187 (1974); Angew. Chem. internat. Edit. *13*, 170 (1974).

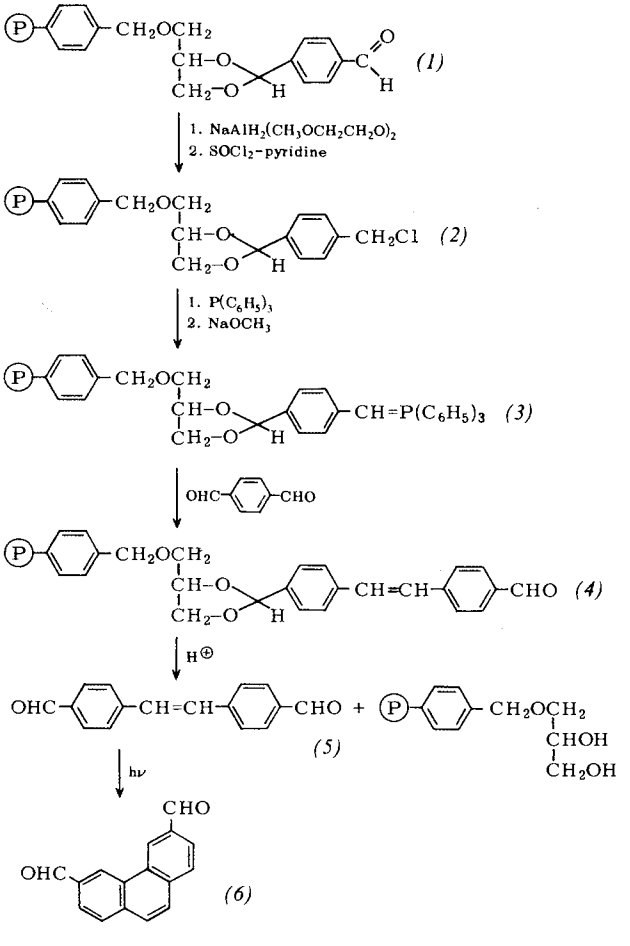
[6] *C. J. Pedersen*, J. Amer. Chem. Soc. *89*, 7017 (1967); *C. J. Pedersen* and *H. K. Frensdorff*, Angew. Chem. *84*, 16 (1972); Angew. Chem. internat. Edit. *11*, 16 (1972); *D. J. Sam* and *H. F. Simmons*, J. Amer. Chem. Soc. *94*, 4024 (1972).

[7] *M. Mąkosza* and *J. Gajos*, Bull. Acad. Pol. Sci., Ser. Sci. Chim. *20*, 33 (1972); *E. V. Dehmlow*, Liebigs Ann. Chem. *758*, 148 (1972).

Solid Phase Synthesis and Photochemistry of 4,4′-Stilbenedicarbaldehyde[1][**]

By *Jack Y. Wong*, *Carl Manning*, and *Clifford C. Leznoff*[*]

The failure of the photocyclization-oxidation reaction of acetylstilbenes to acetylphenanthrenes is well known and has been rationalized in terms of the intervention of the n-π* excited states of the carbonyl group[2, 3]. In contrast to this previous failure we wish to report the photocyclization-oxidation of the closely related 4,4′-stilbenedicarbaldehyde *(5)* to 3,6-phenanthrenedicarbaldehyde *(6)* in high yield. In addition, the dialdehyde *(5)* has now been synthesized in a unique manner by a multistep synthesis based on our reported solid phase method[4, 5].



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[**] This work was supported by the National Research Council of Canada.

Terephthalaldehyde was attached exclusively at one aldehyde group through an acetal linkage to an insoluble cross-linked polystyrene polymer as described previously[4]. Reduction of the polymer-bound terephthalaldehyde *(1)* with sodium dihydrobis(2-methoxyethoxy)aluminate in benzene gave polymer-bound *p*-hydroxymethylbenzaldehyde, which was washed under standard washing conditions, but without acid, to ensure retention of the hydroxymethylbenzaldehyde to the polymer[4]. Halogenation with thionyl chloride in pyridine gave polymer-bound *p*-chloromethylbenzaldehyde *(2)*, which on treatment with excess triphenylphosphane gave the polymer-bound *p*-formylbenzyltriphenylphosphonium salt. Reaction of the salt with sodium methoxide in dimethylformamide furnished the polymer-bound ylide *(3)*. Addition of excess terephthalaldehyde to *(3)* ensured that reaction took place at only one aldehyde site of terephthalaldehyde to give polymer-bound 4,4'-stilbenedicarbaldehyde *(4)*. Cleavage of *(4)* with dilute HCl in dioxane gave 4,4'-stilbenedicarbaldehyde *(5)*[6] in 10% overall yield. Thus insoluble polymer supports can be used in multistep organic synthesis as well as in "repetitive sequential-type synthesis"[5].

Irradiation of 4.3×10^{-4} M solutions of the dialdehyde *(5)* in benzene for 2 days gave pure 3,6-phenanthrenecarbaldehyde *(6)* [(40%, m.p. 213—215°C); MS: M^+, 234 (3%), $M^+ - CHO$, 205 (30%), $M^+ - 2CHO$, 176 (100); IR (KBr): $\nu = 2720$, 1695 cm^{-1}; ^{1}H-NMR ($CDCl_3$): $\delta = 10.30$ (2CHO), 9.22 (H^4, H^5), 8.3—7.8 (H^1, H^8, H^2, H^7, H^9, H^{10}); UV ($CHCl_3$): λ_{max} 258 (35100), 327 nm (11700)]. The structure of *(6)* was supported by the spectral data and elemental analysis.

The ease of photocyclization-oxidation of 4,4'-stilbenedicarbaldehyde *(5)* to 3,6-phenanthrenedicarbaldehyde as compared to the failure of 4-acetylstilbene[2] to photocyclize shows that slight structural modifications (in this case replacement of CH_3 by H and of H by CHO) can have a substantial effect on either the energy levels of the n-π* transition of the carbonyl group or the rate of intersystem crossing. Thus, once again, the danger of predicting the outcome of a chemical reaction on the basis of reactions of similar, but not identical, chemical species has been demonstrated.

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(1): 52760-63-1 / *(2)*: 52760-62-0 / *(3)*: 52760-61-9 / *(4)*: 52760-60-8 / *(5)*: 4720-99-4 / *(6)*: 52760-59-5

[1] The Use of Insoluble Polymer Supports in Organic Synthesis, Part 4. Part 3: Ref. [4]. Photocyclization Reactions of Acyl Polyenes, Part 8. Part 7: *C. C. Leznoff, W. Lilie*, and *C. Manning*, Can. J. Chem. *52*, 132 (1974).

[2] *F. B. Mallory, C. S. Wood*, and *J. T. Gordon*, J. Amer. Chem. Soc. *86*, 3094 (1964).

[3] *E. V. Blackburn* and *C. J. Timmons*, Quart. Rev. Chem. Soc. *23*, 482 (1969).

[4] *C. C. Leznoff* and *J. Y. Wong*, Can. J. Chem. *51*, 3756 (1973).

[5] *C. C. Leznoff*, Chem. Soc. Rev. *3*, 65 (1974).

[6] *G. Drefahl* and *G. Plötner*, Chem. Ber. *91*, 1274 (1958).

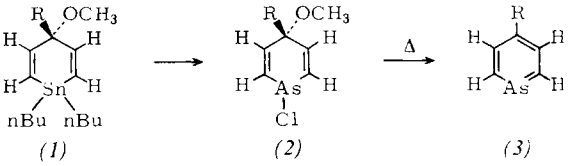
4-Alkoxyarsabenzenes

By *Gottfried Märkl* and *Fritz Kneidl*[*]

Arsabenzenes and phosphabenzenes[1] bearing functional groups have hitherto been unknown. An inquiry into the activity of these groups under the influence of the heteroaromatic ring and *vice versa* would make their synthesis appear particularly desirable.

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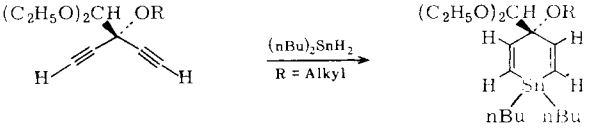
Our recent preparation[2] of arsa- (and phospha)benzenes *(3)* bearing alkyl and aryl substituents in position 4, from 1,4-



(1) *(2)* *(3)*

dihydrostannabenzenes *(1)* *via* the dihydroarsa(phospha)benzene intermediates *(2)*, should provide an entry to arsa(phospha)benzenes with functional groups at position 4, provided that corresponding precursors *(1)* containing the functional group R can be synthesized.

Ethyl 2,2-diethoxyacetate[3] reacts smoothly with ethynylmagnesium bromide to give 3-(diethoxymethyl)-1,4-pentadiyn-3-ol *(4)*, R = H (Table 1). Etherification of *(4)* with dimethyl or diethyl sulfate by the phase transfer method[4] provides ready access to the alkoxy-substituted pentadiynes *(5a)* and *(5b)* (Table 1).



(4), R = H
(5a), R = CH_3
(5b), R = C_2H_5

(6a), R = CH_3
(6b), R = C_2H_5

The pentadiynes *(5)* undergo smooth cycloaddition with di-*n*-butyltin dihydride, giving 4-(diethoxymethyl)-4-alkoxy-substituted 1,4-dihydrostannabenzenes *(6)* (Table 1). The dihydro compounds *(6)* react with $AsCl_3$ in tetrahydrofuran at 75°C to yield the 1-chloro-1,4-dihydroarsabenzenes *(7)* which can be isolated pure by chromatography with chloroform over silica gel (the dibutyltin dichloride is first eluted with benzene) (Table 1).

Table 1. Compounds of type *(4)*—*(8)* prepared.

(4), R = H, m.p. 57—58°C, light yellow needles, yield 90%; ^{1}H-NMR ($CDCl_3$): $-CH_3$: $\tau = 8.74$ (t), $J = 7$ Hz, 6H; $-OCH_2-$: $\tau = 6.17$ (q), $J = 7$ Hz, 2H; $\tau = 6.20$ (q), $J = 7$ Hz, 2H; ≡CH: $\tau = 7.44$ (s), 2H; ≥CH: $\tau = 5.5$ (s), 1H; IR (cap. layer): $\nu_{C\equiv C}$ 2110 cm^{-1}; $\nu_{\equiv CH}$ 3260 cm^{-1}, ν_{OH} 3400 cm^{-1}

(5a), R = CH_3, light yellow oil, chromatographic purification (basic Al_2O_3), yield 78—89%; ^{1}H-NMR ($CDCl_3$): $-CH_3$: $\tau = 8.8$ (t), $J = 7$ Hz, 6H; $-OCH_2-$: $\tau = 6.2$ (q), $J = 7$ Hz, 4H; $-OCH_3$: $\tau = 6.5$ (s), ≡CH: $\tau = 7.40$ (s), 2H; ≥CH: $\tau = 5.50$ (s), 1H; IR (cap. layer): $\nu_{C\equiv C}$ 2120 cm^{-1}; $\nu_{\equiv CH}$ 3270 cm^{-1}; acetal stretching vibration: 1085, 1120 cm^{-1}

(5b), R = C_2H_5, light yellow oil, yield 77%; ^{1}H-NMR ($CDCl_3$): $-CH_3$: $\tau = 8.77$ (t), 8.80 (t), $J = 7$ Hz, 9H; $-OCH_2-$: $\tau = 6.24$ (q), $J = 7$ Hz, 6H; ≡CH: $\tau = 7.45$ (s), 2H; ≥CH: $\tau = 5.55$ (s), 1H; IR (cap. layer): $\nu_{C\equiv C}$ 2125 cm^{-1}; $\nu_{\equiv CH}$ 3270 cm^{-1}

(6a), R = CH_3, light yellow highly refractive oil, purification by bulb tube distillation, yield 59%; ^{1}H-NMR ($CDCl_3$): $-CH_3$, $-CH_2-$: $\tau = 8.20$—9.20 (m), 24H; $-OCH_3$: $\tau = 6.80$ (s); $-OCH_2-$: $\tau = 6.28$ (q), 2H; $\tau = 6.34$ (q) 2H, $J = 7$ Hz; ring-H: $\tau = 3.54$ (s); 2.7H; ^{117,119}Sn satellites: 109 Hz, 90 Hz, 54 Hz, *ca.* 1.3H; ≥CH: $\tau = 5.77$ (s), 1H; IR (cap. layer): $\nu_{C=C}$ 1600 cm^{-1}, acetal stretching vibration 1115, 1080, 1065, 1050 cm^{-1}

(6b), R = C_2H_5, light yellow oil, bulb tube distillation, yield 56%; ^{1}H-NMR ($CDCl_3$): $-CH_3$, $-CH_2-$: $\tau = 8.20$—9.20 (m), 27H; $-OCH_2-$: $\tau = 6.25$ (q), 2H; $\tau = 6.77$ (q), 4H; ≥CH: $\tau = 5.77$ (s), 1H; ring-H: $\tau = 3.56$ (s); 2.6H; ^{117,119}Sn satellites: 104 Hz, 84 Hz, 52 Hz, *ca.* 1.4H

(7a), R = CH_3 light yellow oil, yield 55%; ^{1}H-NMR ($CDCl_3$): $-CH_3$: $\tau = 8.80$ (t), $J = 7$ Hz, 6H; $-OCH_2-$: $\tau = 6.34$ (q), 2H; $\tau = 6.38$ (q), 2H, $J = 7$ Hz; $-OCH_3$: $\tau = 6.64$ (s); ≥CH: $\tau = 5.79$ (s); ring-H: AB spectrum, H_A: $\tau = 2.98$, H_B: $\tau = 3.60$, $J_{AB} = 11$ Hz

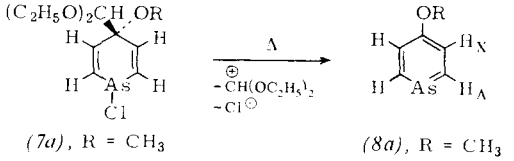
Table 1 *(Continued)*.

(7b), R = C_2H_5, light yellow oil, yield 57 %: same ring proton AB spectrum as for *(7a)*

(8a), R = CH_3, light yellow oil, yield 52 %: ^{1}H-NMR ($CDCl_3$): $-OCH_3$: $\tau = 6.17$ (s); ring protons, A_2X_2 spectrum, H_A: $\tau = 0.37$ (d), H_X: $\tau = 2.40$ (d), $J = 12$ Hz [in 4-methoxypyridine the signals of the ring protons lie at significantly higher field: A_2X_2 spectrum, H_A: $\tau = 1.68$, H_X: $\tau = 3.29$, $J = 6$ Hz; $-OCH_3$: $\tau = 6.27$ (s)]; IR (cap. layer): =CH stretching: 3050, 3020 cm^{-1}; ring stretching: 1550, 1470, 1400 cm^{-1}; C—O stretching: 1245, 1030 cm^{-1} [in 4-methoxypyridine the =CH and C=C stretching bands lie at significantly higher wave numbers: =CH stretching 3070, 3040 cm^{-1}; ring stretching 1590, 1570 cm^{-1}]: UV (ethanol): λ_{max} 223 nm (ε 8900); 287 nm (ε 11000) [significant bathochromic shift compared to unsubstituted arsenin (λ_{max} 219, 268 nm)]; mass spectrum (70 eV): M^+ (C_6H_5AsO) 170 (100 %); $[M-CH_3]^+$ 155 (8 %); $[M-CH_2O]^+$ 140 (13 %); $[155-CO]^+$ 127 (35 %); $[M-As]^+$ 95 (34 %)

(8b), R = C_2H_5, light yellow oil, yield 44 %; ^{1}H-NMR ($CDCl_3$): $-CH_3$: $\tau = 8.60$ (t), $J = 7$ Hz; $-OCH_2-$: $\tau = 5.94$ (q), $J = 7$ Hz; ring protons: A_2X_2 spectrum, H_A: $\tau = 0.34$ (d), H_X: $\tau = 2.60$ (d), $J = 11$ Hz; IR (cap. layer): =CH stretching: 3060, 3020 cm^{-1}; ring stretching: 1540, 1470, 1395 cm^{-1}; C—O stretching: 1230, 1035 cm^{-1}; UV (ethanol): λ_{max}: 226 nm (ε 15100), 291 nm (ε 18000); mass spectrum (70 eV): M^+ (C_8H_9AsO) 184 (91 %); $[M-C_2H_4]^+$ 156 (100 %); $[156-CO]^+$ 128 (38 %); $[156-As]^+$ 81 (93 %)

Thermolysis of the dihydroarsabenzenes *(7)* takes an unexpected course. Whereas thermolysis of the dihydroarsabenzenes *(2)* yields the 4-substituted arsabenzenes *(3)* (it remaining open whether the 1,4-elimination of the methoxy group and the chlorine proceeds *via* a free-radical or an ionic mechanism, and which substituents act as nucleofugal or electrofugal leaving group in the latter case), in the dihydroarsabenzenes *(7)* the formyl acetal group is the better, apparently cationic, leaving group; decomposition at 140 °C affords exclusively the 4-alkoxyarsabenzenes (4-alkoxyarsenins) *(8)* (Table 1).



(7a), R = CH_3; *(7b)*, R = C_2H_5 — *(8a)*, R = CH_3; *(8b)*, R = C_2H_5

The fragmentation patterns apparent from the mass spectra are in complete correspondence with those of phenyl ethers. The 4-hydroxyarsabenzene ("arsaphenol") cation observed in the spectrum of *(8b)* decomposes in the same manner as the phenols with loss of CO. Attempts to convert the 4-alkoxyarsabenzenes *(8)* into the corresponding 4-hydroxyarsabenzene, an "arsaphenol", *via* ether cleavage have so far remained unsuccessful.

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(4): 52748-36-4 / *(5a)*: 52748-37-5 / *(5b)*: 52748-38-6 / *(6a)*: 52748-39-7 / *(6b)*: 52748-40-0 / *(7a)*: 52748-41-1 / *(7b)*: 52748-42-2 / *(8a)*: 52748-43-3 / *(8b)*: 52748-44-4 / $(n\text{-Bu})_2SnH_2$: 1002-53-5.

[1] *G. Märkl*, Angew. Chem. 78, 907 (1966); Angew. Chem. internat. Edit. 5, 846 (1966); *A. J. Ashe III*, J. Amer. Chem. Soc. 93, 3293 (1971); *K. Dimroth*, Fortschr. Chem. Forsch. 38, 20 (1973).

[2] *G. Märkl* and *F. Kneidl*, Angew. Chem. 85, 990 (1973); Angew. Chem. internat. Edit. 12, 931 (1973).

[3] *R. B. Moffett*, Org. Synth. Coll. Vol. IV, 427 (1967).

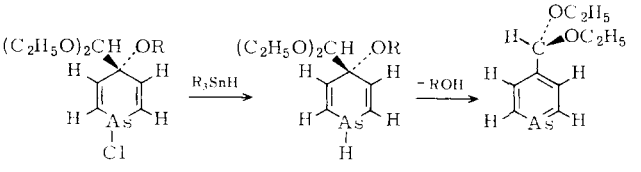
[4] *A. Merz*, Angew. Chem. 85, 868 (1973); Angew. Chem. internat. Edit. 12, 846 (1973).

Arsabenzene-4-carbaldehyde

By *Gottfried Märkl* and *Fritz Kneidl*[*]

Whereas thermolysis of 1-chloro-4-methoxy-4-alkyl(aryl)-1,4-dihydroarsabenzenes leads *via* loss of the methoxy group and the halogen to 4-substituted arsabenzenes[1], in the case of the 4-alkoxy-1-chloro-4-(diethoxymethyl)-1,4-dihydroarsabenzenes *(1)* the diethoxymethyl group proves to be the better (probably electrofugal) leaving group; thermolysis affords 4-alkoxyarsabenzenes[2].

Reduction of the 1-chloro-1,4-dihydroarsabenzenes *(1)* with trialkyltin hydride to give 1,4-dihydroarsabenzenes *(2)* provides a means of reversing the polarity of the leaving groups. The dihydro compounds *(2)* resist all attempts at detection. Under the conditions of their formation compounds *(2)* undergo 1,4-elimination of ethanol or methanol to form the diethyl acetal of arsabenzene-4-carbaldehyde (4-(diethoxymethylarsabenzene) *(3)* (Table 1).



(1), R = CH_3, C_2H_5 — *(2)*, R = CH_3, C_2H_5 — *(3)*

Table 1. Compounds *(3)*, *(4)*, and *(5)* prepared.

(3), light yellow oil, purification by distillation in a bulb tube at 10^{-2} torr, yield 47–52 %: ^{1}H-NMR ($CDCl_3$): $-CH_3$: $\tau = 8.77$ (t), 6H, $J = 7$ Hz; $-OCH_2-$: $\tau = 6.44$ (q), 4H, $J = 7$ Hz; ≡CH: $\tau = 4.54$ (s); ring protons: A_2X_2 spectrum: H_A: $\tau = 0.07$ (d), 2H; H_X: $\tau = 1.94$(d), 2H, $J = 11$ Hz; UV (ethanol): λ_{max} 225 nm (ε 7700), 299 nm (ε 8800); IR (cap. layer): $\nu_{CH(aromatic)}$ 3010 cm^{-1}, $\nu_{C=C}$ 1555 cm^{-1}, $\nu_{CH(aliphatic)}$ 2960, 2920, 2860 cm^{-1}; acetal stretching vibration: 1045, 1085, 1100 cm^{-1}

(4), light yellow oil, yield 70 %: ^{1}H-NMR ($CDCl_3$): ring protons: A_2X_2 spectrum: H_A: $\tau = 0.07$ (d), 2H; H_X: $\tau = 1.67$ (d), 2H, $J = 12$ Hz; —CHO: $\tau = -0.03$ (s), 1H; the aldehyde proton lies in the downfield branch of the H_A doublet; resolution is accomplished in acetone: H_A: $\tau = 0.46$ (d), 2H; H_X: $\tau = 2.10$ (d), 2H, $J = 12$ Hz; —CHO: $\tau = 0.46$ (s), 1H; IR (cap. layer): =CH stretching: 3040, 2970 cm^{-1}, *CHO* stretching: 2840, 2740 cm^{-1}, C=O stretching: 1685, ring stretching: 1560, 1490, 1360 cm^{-1} [4-pyridinecarbaldehyde: =CH stretching: 3060, 3000 cm^{-1}, *CHO* stretching: 2860, 2760 cm^{-1}, C=O stretching: 1710 cm^{-1}, ring stretching: 1600, 1570, 1490, 1415, 1400 cm^{-1}; benzaldehyde: CO stretching: 1700 cm^{-1}]; UV (ethanol): λ_{max} 229 nm (ε 10900), 300 nm (ε 16200) [arsabenzene: λ_{max} 219 nm (ε 15000), 268 nm (ε 11000); 4-pyridinecarbaldehyde: λ_{max} 220 nm (ε 2550 sh), 256 nm (3300)]; mass spectrum: M^+ (C_6H_5AsO) 168 (44 %); $[M-1]^+$ 167 (15 %); $[M-CO]^+$ 140 (62 %); $[(M-1)-CO]^+$ 139 (37 %); $[139-C_2H_2]^+$ 113 (100 %); $[113-1H]^+$ 112 (64 %)

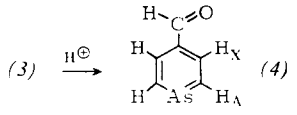
(5), light yellow oil (chromatography on Al_2O_3), which solidifies to a crystalline mass in the cold: ^{1}H-NMR ($CDCl_3$): $-CH_3$: $\tau = 7.83$ (s), 3H; —OH: $\tau = 7.6$ (s), 1H; $-CH_2-$: $\tau = 7.14$ (d), $J = 6$ Hz; ≡CH: $\tau = 4.81$ (t), $J = 6$ Hz; ring protons: A_2X_2 spectrum: H_A: $\tau = 0.17$ (d), H_X: $\tau = 2.1$ (d), $J = 11$ Hz

Under the reaction conditions used for reduction of the 4-methoxy-1,4-dihydroarsabenzene derivative *(1)*, R = CH_3, rapid exchange occurs between the diethyl acetal *(3)* and the methanol formed by 1,4-elimination. According to the ^{1}H-NMR spectrum, the reaction mixture contains only 50 % of the diethyl acetal, alongside 9 % of the dimethyl acetal and 41 % of the ethyl methyl acetal.

The diethyl acetal *(3)* undergoes extremely rapid cleavage, quantitative reaction being complete within 15 min in the presence of an acidic ion exchanger in moist acetone solution.

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Arsabenzene-4-carbaldehyde *(4)* can be obtained pure as a pale yellow oil by bulb tube vacuum distillation (10^{-2} torr). Surprisingly, the product, which is stable under nitrogen, smells strongly and unmistakably of benzaldehyde, thus providing further justification for the trivial name "arsabenzaldehyde"

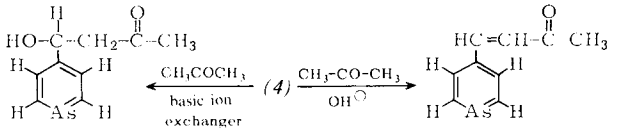


(3) $\xrightarrow{H^{\oplus}}$ *(4)*

The chemical shift of the aldehydic proton of *(4)* lies almost unchanged in the range corresponding to aromatic aldehydes. In contrast, the signals of the ring protons display a pronounced downfield shift, probably as a result of As anisotropic effects. Benzaldehyde and arsabenzaldehyde *(4)* exhibit an almost identical solvent dependence of the chemical shift.

The mass spectrum of "arsabenzaldehyde" *(4)* shows the characteristic fragments of aromatic aldehydes, the fragmentation pattern being practically identical with that of benzaldehyde[3].

Preliminary experiments reveal a normal electrophilic reactivity of the aldehyde group. In the presence of basic ion exchangers, *(4)* undergoes a normal aldol reaction with acetone to give the alcohol *(5)* (Table 1). Aldol condensations of *(4)* with aldehydes and ketones can also be performed in the presence of strong alkalis. Thus *(4)* reacts with acetone on addition of 20% caustic soda to give arsabenzylideneacetone *(6)* directly.



(5) ← CH_3COCH_3, basic ion exchanger — *(4)* — CH_3-CO-CH_3, $OH^{\ominus}$ → *(6)*

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CAS Registry Numbers:
(3): 52748-28-4 / *(4)*: 52748-29-5 / *(5)*: 52748-30-8

[1] *G. Märkl* and *F. Kneidl*, Angew. Chem. 85, 990 (1973); Angew. Chem. internat. Edit. 12, 931 (1973).

[2] *G. Märkl* and *F. Kneidl*, Angew. Chem. 86, 745 (1974); Angew. Chem. internat. Edit. 13, 667 (1974).

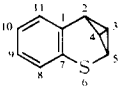
[3] *J. D. McCollum* and *S. Meyerson*, J. Amer. Chem. Soc. 85, 1739 (1963).

X-Ray Structure Analysis of 6-Thiatetracyclo-[5.4.0.0^{2,4}.0^{3,5}]undeca-1(7),8,10-triene

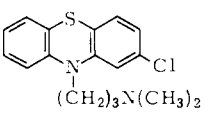
By *Chizuko Kabuto*, *Toshio Tatsuoka*, *Ichiro Murata*, and *Yoshio Kitahara*[*]

We have recently reported on the preparation and reactivity of the novel compound 6-thiatetracyclo[5.4.0.0^{2,4}.0^{3,5}]undeca-1(7),8,10-triene *(1)*[1], in which the highly strained bicyclo[1.1.0]butane moiety is incorporated in a sulfur-containing conjugated framework. We have now carried out an X-ray structure analysis of *(1)* in order to establish the geometrical features of the bicyclobutane system[2, 3] and to gain a knowledge of the nature of the CS bonding[4].

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(1)



(2)

(1) crystallizes in the orthorhombic space group $P2_12_12_1$ with $a=6.493$, $b=14.690$, $c=8.309$ Å, and $Z=4$. A total of 1110 reflections were measured on a single crystal (*ca.* $0.2\times0.2\times0.3$ mm^3) using an automated Rigaku four-circle diffractometer with $Mo_{K\gamma}$ radiation.

The structure was solved by a heavy atom method and refined by a block-diagonal least-squares method. After several cycles of refinement with anisotropic temperature factors for the C and S atoms and isotropic temperature factors for the hydrogen atoms, which were located from a difference map, the refinement converged to give an *R*-factor of 0.044 for all non-zero reflections.

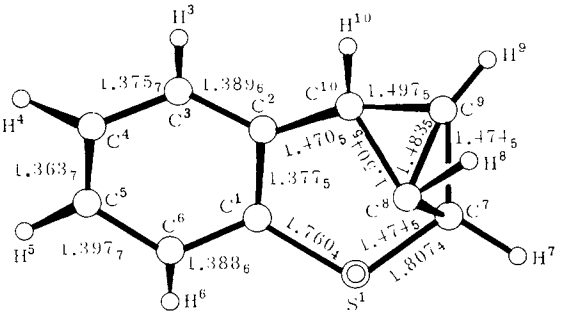


Fig. 1. The molecular structure of *(1)*, viewed along the *c* axis. The bond lengths (Å) and their standard deviations ($\times10^{-3}$ Å) are shown. A few bond angles (°) are as follows:

C^1—S^1—C^7	= 100.3(0.2)	C^8—C^9—C^{10}	= 60.8(0.3)
S^1—C^1—C^2	= 121.2(0.4)	C^7—C^9—C^{10}	= 98.9(0.4)
S^1—C^1—C^6	= 117.5(0.4)	C^2—C^{10}—C^9	= 120.9(0.4)
S^1—C^7—C^8	= 122.3(0.4)	C^2—C^{10}—C^9	= 121.6(0.4)
S^1—C^7—C^9	= 121.3(0.4)	C^8—C^{10}—C^9	= 59.0(0.3)
C^8—C^7—C^9	= 60.3(0.3)	S^1—C^7—H^7	= 105.6(2.6)
C^9—C^8—C^{10}	= 60.2(0.3)	C^2—C^{10}—H^{10}	= 117.1(2.7)
C^7—C^8—C^{10}	= 98.6(0.5)	H^8—C^8—$C^{7,9,10}$ and	
C^7—C^9—C^8	= 59.8(0.3)	H^9—C^9—$C^{7,8,10}$	= 128 to 133(3)

As shown in Fig. 1, the whole molecule is rather rigid and constrained. The benzene ring is planar and S^1, C^{10}, and C^7 atoms lie almost completely on this plane; the maximum deviation from the best plane through the benzene ring and S^1, C^{10}, and C^7 is 0.039 Å for C^7. C^8 and C^9 deviate by 0.74 Å from this plane. The dihedral angle of 122 between the two cyclopropane rings is similar to that in free bicyclobutane[2].

The two C—S bonds differ in length. The length of C^1—S^1 (1.760 Å) agrees well with that for a C(sp^2)—S bond[5]: for example in chloropromazine the length is 1.75 Å, which has been postulated to have 13% double bond character[6]. In contrast, the length of C^7—S^1 (1.808 Å) compares favorably with that for a C(sp^3)—S bond, as found in dimethyl sulfide (1.803 Å)[7]. This bond would be shorter if the carbon atom—as postulated in cyclopropane—were to be sited in an $sp^{2.2}$ hybridization orbital. The length of the C^2—C^{10} bond (1.470 Å), which is about the same as that of the C(sp^2)—C(sp^2) bond (1.48 Å), clearly indicates such an effect.

The bonds C^7—C^8 and C^7—C^9 (both 1.474 Å) are appreciably shorter than the analogous bonds C^8—C^{10} and C^9—C^{10}. For comparison: the corresponding bond to the latter in free bicyclobutane is 1.498 Å[2].

From these findings it may be concluded that the neighboring sulfur atom may change the bonding character in *(1)*, *i.e.*, for example, increase the p-character in the C^7—S^1 bond and correspondingly decrease the p-character in the C^7—C^8 and C^7—C^9 bonds. The bond angle S^1—C^7—H^7 (105.6°) is compatible with such changes in the orbitals.

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CAS Registry Number:
(1): 51459-54-2.

[1] *I. Murata, T. Tatsuoka*, and *Y. Sugihara*, Tetrahedron Lett. *1973*, 4261; *1974*, 199; Angew. Chem. *86*, 161 (1974); Angew. Chem. internat. Edit. *13*, 142 (1974).

[2] *K. W. Cox, M. D. Harmony, G. Nelson*, and *K. B. Wiberg*, J. Chem. Phys. *50*, 1976 (1969).

[3] *J. Trotter, C. S. Gibbons, N. Nakatsuka*, and *S. Masamune*, J. Amer. Chem. Soc. *89*, 2792 (1967); *R. D. Suenram* and *M. D. Harmony*, *ibid.* *95*, 4506 (1973).

[4] On the nature of CS bonds see *e.g. C. C. Price* and *S. Oae*: Sulfur Bonding. Ronald Press, New York 1962.

[5] *J. P. Schaefer* and *L. L. Reed*, J. Amer. Chem. Soc. *94*, 908 (1972).

[6] *J. J. H. McDowell*, Acta Crystallogr. *B 25*, 2175 (1969).

[7] *W. Maier*, Angew. Chem. *73*, 120 (1961).

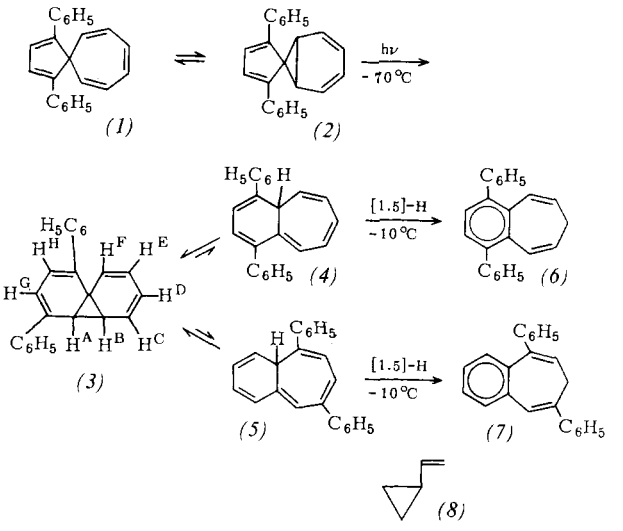
Photochemical Synthesis of a Tricyclo[5.4.0.0^{1,6}]-undecatetraene in Solution[**]

By *Heinz Dürr, Michael Kausch*, and *Helge Kober*[*]

An explanation of the photolysis of diazocyclopentadienes in benzene requires postulation of an intermediate *(3)* (designated as a "bisnorcaradiene" in ref. [1])[1]. This reaction proceeds *via* the unsaturated spiro compounds *(1)*, which are in equilibrium with their valence isomers, the spiro[cyclopentadienenorcaradienes] *(2)*.

In the present communication we describe the photochemical synthesis of 2,5-diphenyltricyclo[5.4.0.0^{1,6}]undeca-2,4,8,10-tetraene *(3)* in solution.

A 20-mg sample of the valence isomer mixture *(1)*⇌*(2)* in $CDCl_3$/Frigen 11 (1:1, 0.5 ml) was placed in an NMR sample tube and irradiated with a monochromator ($\lambda = 360$ nm) for 2 h at -70 ± 2 °C in a specially constructed Cu low temperature cell. This led to a yellowish solution containing only *(3)* (TLC and NMR indicate no further products). ^{1}H-NMR spectra of this solution were recorded by the PFT method and the CW technique[3]. At −60 °C the spectrum contains a doublet for H^A at $\delta = 2.87$ ppm ($^3J = 9.0$ Hz) and a doublet of doublets for H^B at 4.62 ppm ($^3J = 6.2$ and 9.0 Hz) in the ratio 1:1. The remaining signals are to be assigned to H^C (6.40 ppm), H^F (6.24 ppm), and the $H^{E.D.H.G}$ protons (6.4—7.2 ppm) (7.2—7.6 ppm aromatic H). All signals are broadened by long range coupling. Double resonance experiments show that irradiation at the resonance frequency of H^B leads to a singlet for H^A, while irradiation at the frequency of H^A simplifies the signal of H^B to a doublet. The assignment of H^A and H^B accords well with the δ- and *J*-values for vinylcyclopropane *(8)*[2]. The UV spectrum (*n*-pentane) of *(3)* displays maxima at 288 ($\varepsilon = ca.$ 30000) and 415 ($\varepsilon = ca.$ 7500) nm.



Cooling of the NMR sample from −20 to −90 °C leads to no change in the spectrum of *(3)*. Hence it follows that the equilibrium *(4)*⇌*(3)*⇌*(5)*[4] lies completely on the side of *(3)*. If the solution of *(3)* in $CDCl_3$/Frigen 11 is heated to −10 °C thermal rearrangement occurs to give the benzocycloheptenes *(6)* and *(7)*, which have been previously described in ref. [1]. Valence isomerization first takes place to form *(4)* and *(5)*, which are then transformed by sigmatropic [1.5]H shift to *(6)* and *(7)*. A kinetic study of the thermolysis of *(3)* using UV spectroscopy afforded the activation parameters of the reaction *(3)* → *(6)* + *(7)*: $E_A = 15.8 \pm 0.4$, $\Delta G^{\neq} = 21.5 \pm 0.4$, $\Delta H^{\neq} = 15.2 \pm 0.4$ kcal/mol; $\Delta S^{\neq} = -21 \pm 2$ cal deg^{-1} mol^{-1}. The half-life of *(3)* at 21 °C is 16 min; the reaction *(3)* → *(6)* + *(7)* is of first order.

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[1] *H. Dürr, H. Kober, I. Halberstadt, U. Neu, T. T. Coburn, T. Mitsuhashi*, and *W. M. Jones*, J. Amer. Chem. Soc. *95*, 3818 (1973); cf. also *T. Mitsuhashi* and *W. M. Jones*, J. C. S. Chem. Comm. *1974*, 103.

[2] *H. Günther* and *D. Wendisch*, Chem. Ber. *104*, 3914 (1971).

[3] The CW technique is the normally employed method utilizing a continuous change of the resonance frequency (continuous wave).

[4] The isomers *(4)* and *(5)* have been described by *H. Dürr* and *G. Scheppers*, Liebigs Ann. Chem. *734*, 141 (1970), and also by *G. W. Gruber* and *M. Pomerantz*, Tetrahedron Lett. *1970*, 3755, who formulated *(3)* as a mechanistic possibility.

Antimony(V)-Transition Metal Compounds with Covalent and Ionic Character

By *Wolfgang Malisch* and *Peter Panster*[*]

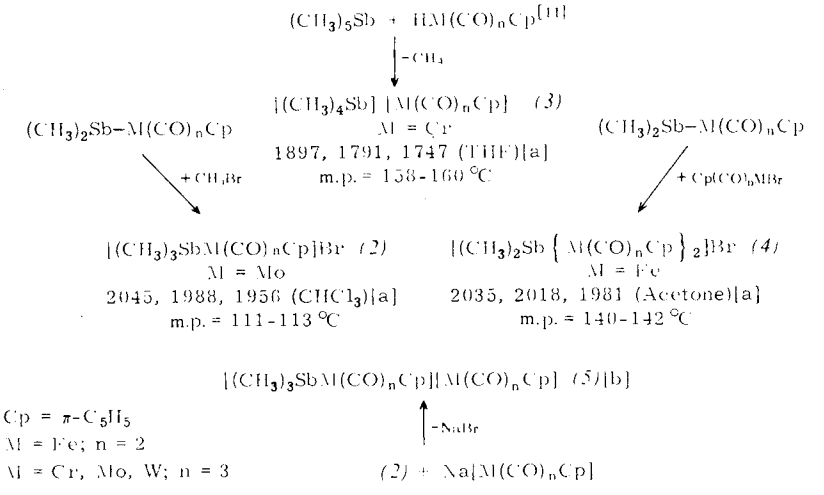
During our studies on the reactivity of dialkylarsenido- and dialkylantimonido-transition metal compounds, which are capable of existence as mononuclear complexes[1, 2], we have found that the action of halogen, *e.g.* bromine, leads to oxidative addition of agent with formation of metal-substituted element(V) dihalides, and not, as in comparable systems, to the cleavage of the element-metal or element-carbon bond[3]. Complexes of this type have previously been postulated only as short-lived intermediate compounds[4].

The antimony(V) derivatives *(1)* of metals of the VIth subgroup are particularly readily accessible; they are generally obtained directly under mild reaction conditions (20 °C, cyclo-

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[**] Photochemistry of Small Rings, Part 32.—Part 31: *H. Dürr, A. C. Ramade*, and *I. Halberstadt*, Tetrahedron Lett. *1974*, 3041.—This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

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Scheme 1. Antimony(v)-metal complexes with ionic character.
[a] ν_{CO} [cm^{-1}], NaCl cell (solvent).
[b] Complex antimony metalates of this type are capable of existence only momentarily in solution.

hexane, high dilution) as yellow crystals which are only slightly soluble in non-polar solvents[5].

$$\pi\text{-}C_5H_5(CO)_3M\text{–}Sb(CH_3)_2 + Br_2 \longrightarrow \pi\text{-}C_5H_5(CO)_3M\text{–}SbBr_2(CH_3)_2 \quad (1)$$

(1)

Table 1. Properties of the transition metal-antimony(v) dibromides *(1)*.

	M [a]	M.p. [b] [°C]	^{1}H-NMR [c] $\delta_{C_5H_5}$ [Hz] (s, 5H)	δ_{CH_3} [Hz] (s, 6H)	IR [d] ν_{CO} [cm^{-1}]
(1a)	Cr	above 88	−321	−163.5	2034 1971
(1b)	Mo	91–93	−347	−162	2047 1977
(1c)	W	114–116	−356	−165.5	2043 1961

[a] Composition by elemental analysis.
[b] Closed capillary (Cu block). All complexes melt with decomposition.
[c] $CDCl_3$ solution, TMS internal (60 MHz).
[d] NaCl cell ($CHCl_3$). The long-wave bands have broad structure.

The complexes *(1)* are monomeric in solution, and, according to conductivity measurements, only insignificantly dissociated [*e.g. (1c)*: mol.wt. (cryoscopically in $CHBr_3$) 639 (calc. 644.6); $\Lambda = 1.29\ \Omega^{-1}\ mol^{-1}\ cm^2$ (0.02 M in acetone)[6]]. Their chemical behavior, like that of the trimethylantimony dihalides[7], is determined by the tendency of the central atom to acquire tricoordination *via* ligand elimination.

$$Br_2(CH_3)_2Sb\text{–}Mo(CO)_3\pi\text{-}C_5H_5 \longrightarrow \quad (2)$$
(1b)

$$(CH_3)_2SbBr + \pi\text{-}C_5H_5(CO)_3MoBr$$

This reaction occurs under solvolytic and thermal conditions as well as under mass spectroscopic conditions, and, together with the reaction of formation (1), shows that the halogen-cleavage in such element-transition metal compounds must be regarded as an addition-elimination process. The observed dependence of the rate of decomposition on the nature of the metal and element atoms (Fe≫Mo>Cr>W; As≫Sb) precludes complete characterization of the adducts in critical cases (Fe—Sb or M—As).

Such a reaction behavior confirms the pentacoordination of the central atom and, together with spectral data[8], would strongly suggest a covalent structure of trigonal-bipyramidal geometry for this type of compound, as has already been demonstrated for molecules having the composition $(CH_3)_3SbX_2$[9]. The proposed ligand arrangement is in agreement with the polarity rules applicable to such coordination polyhedra[10]. A prerequisite for realization of covalency in antimony(v)-metal complexes is the incorporation of at least two halogen atoms per molecule. Their successive replacement by methyl [*(2)*, *(3)*] or metal groups [*(4)*, *(5)*] yields exclusively purely ionic products (Scheme 1).

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(1a), 52571-28-5; *(1b)*, 52571-29-6; *(1c)*, 52571-30-9; *(2)*, 52571-31-0; *(3)*, 52571-32-1; *(4)*, 52571-33-2; $(CH_3)_2Sb$–$Cr(CO)_3Cp$, 52571-34-3; $(CH_3)_2Sb$–$Mo(CO)_3Cp$, 52571-35-4; $(CH_3)_2Sb$–$W(CO)_3Cp$, 52571-36-5; $(CH_3)_2Sb$–$Fe(CO)_2Cp$, 52571-37-6; $HCr(CO)_3Cp$, 36495-37-1; $Cp(CO)_2FeBr$, 12078-20-5; $(CH_3)_5Sb$, 15120-50-0; CH_3Br, 74-83-9.

[1] Metal-Substituted VB-Element Systems Part 4. Part 3: *W. Malisch* and *P. Panster*, J. Organometal. Chem. 7, C7 (1974).

[2] *W. Malisch* and *M. Kuhn*, Angew. Chem. *86*, 51 (1974); Angew. Chem. internat. Edit. *13*, 84 (1974).

[3] *R. D. Gorsich*, J. Amer. Chem. Soc. *84*, 2486 (1962); *B. J. Aylett* and *J. M. Campbell*, J. Chem. Soc. *A 1969*, 1910.

[4] *W. R. Cullen*, *D. J. Patmore*, and *J. R. Sams*, Inorg. Chem. *12*, 867 (1973).

[5] Bismetalated antimony(v) dibromides can be prepared by the same method *e.g.* $CH_3Sb[W(CO)_3\pi\text{-}C_5H_5]_2Br_2$, decomp. above 58 °C but are considerably less stable than *(1)*.

[6] For $(CH_3)_3SbCl_2$, $\Lambda = 3.24\ \Omega^{-1}\ mol^{-1}\ cm^2$ (CH_3CN). *T. M. Lowry* and *H. I. Simons*, Ber. Deut. Chem. Ges. *63*, 1595 (1930).

[7] *G. T. Morgan* and *G. R. Davies*, Proc. Roy. Soc. London *A 110*, 523 (1926).

[8] The NMR-spectroscopical equivalence of the methyl groups would also be guaranteed in the case of rapid site exchange processes or in a *trans*-axial arrangement. No change was seen in the the signals on going down to −80 °C.

[9] *K. Shen*, *W. E. McEwen*, *S. J. LaPlaca*, *W. C. Hamilton*, and *A. P. Wolf*, J. Amer. Chem. Soc. *90*, 1718 (1968), and literature cited therein.

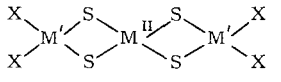
[10] *R. J. Gillespie*, J. Chem. Educ. *47*, 18 (1970).

[11] For the reaction of $Sb(CH_3)_5$ with CH-acidic compounds cf. *H. Schmidbaur, K.-H. Mitschke*, and *J. Weidlein*, Z. Anorg. Allg. Chem. *386*, 147 (1971), and literature cited therein.

Coordination in Bis(thiooxomolybdato)metalate(II) Complexes of Type $[M(MoOS_3)_2]^{2-}$ and $[M(MoO_2S_2)_2]^{2-}$

By *E. Königer-Ahlborn* and *Achim Müller*[*]

Complex anions of the type $[M(WS_4)_2]^{2-}$ [1, 2] and $[M(MoS_4)_2]^{2-}$ [3] contain the structural unit *(1)* (M^{II} = transition metal; M' = Mo^{VI}, W^{VI}; X = S).



(1)

We have now looked into the question of whether thiooxomolybdates also form the corresponding complexes and whether coordination is preferred *via* oxygen *or* sulfur or an isomeric mixture is formed, as in the case of thiosulfato complexes[4]. Using *Pearson*'s theory the type of coordination is not predictable for complexes with Ni or Co as central atom M.

We have now succeeded in isolating and characterizing the following complexes as tetraphenylphosphonium salts by elemental analysis, IR spectra, electron absorption spectra, and magnetic measurements: $[Zn(MoOS_3)_2]^{2-}$ *(2)*, $[Ni(MoOS_3)_2]^{2-}$ *(3)*, $[Ni(MoO_2S_2)_2]^{2-}$ *(4)*, and $[Co(MoO_2S_2)_2]^{2-}$ *(5)*.

(2), *(3)*, and *(4)* are diamagnetic, while *(5)* has a magnetic moment of 4.0 μ_B (at 295 °K). This suggests the likelihood of a square-planar coordination for the niccolates *(3)* and *(4)* and a tetrahedral coordination for the cobaltate *(5)*.

The electron absorption spectra show d→d transitions along with ligand internal charge transfer bands of the type π(S)→d(Mo) and charge transfer bands π(S)→d(M) (M = Ni, Co). Assignment of the bands is possible only if one assumes negligible interactions between the ligand internal MOs and the AOs of the central atom M. The spectra of *(3)* and *(4)* show the spin-allowed transitions expected for a square-planar NiS_4 chromophore (d^8)[5, 6]; the position of the d→d transition $\nu_1(^1A_{1g} \rightarrow {}^1A_{2g})$ suggests that the ligand field strengths of $MoOS_3^{2-}$ and $MoO_2S_2^{2-}$ are of the same order of magnitude as that of the diethyldithiophosphinate ion[6]. The spectrum of *(5)* exhibits a d→d transition at 14900 cm^{-1}, which lies at about the same energy as in compounds having a tetrahedral CoS_4 chromophore[7].

In tetrathiomolybdato complexes the terminal stretching vibrations $\nu(MoS)_t$ appear at ≈500 cm^{-1} and the bridge stretching vibrations at ≈450 cm^{-1}. Interpretation of the spectra of the corresponding metal-isotope substituted compounds ($^{58/62}Ni$) shows that $\nu(MoS)_t$ is practically not coupled with $\nu(MoS)_{br}$[8]. Thus it follows that bands at ≈500 and ≈450 cm^{-1} may be regarded as an indication of the presence of terminal and bridge MoS bonds respectively. The measured frequencies of the stretching vibrations of *(2)*, *(3)*, *(4)*, and *(5)* are listed in Table 1.

Our investigations show, therefore, that, if oxygen and sulfur atoms are present in complexes of the type $[M(MX_nY_m)_2]^{2-}$ (X = O, Y = S; n = 1 or 2, m = 3 or 2) only the sulfur atoms are used for coordination to the central atom M.

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Table 1. Stretching vibrations in the IR spectra of the bis(thiooxomolybdato)-metalates *(2)*—*(5)* (in cm^{-1}).

Complex	$\nu(MoO)$	$\nu(MoS)_t$	$\nu(MoS)_{br}$	$\nu(MS)$ [b]
$[Zn(MoOS_3)_2]^{2-}$ *(2)*	898	502	456, 437	288
$[Ni(MoOS_3)_2]^{2-}$ *(3)*	896	500	458	326
	884	492	446	
$[Ni(MoO_2S_2)_2]^{2-}$ *(4)*	896	— [a]	463	325
	880		453	
$[Co(MoO_2S_2)_2]^{2-}$ *(5)*	903	—	453	289
	884		447	

[a] Very weak band at 498 cm^{-1}.
[b] M = Zn, Ni or Co.

Experimental:

(2) and *(3)*: An aqueous solution of $ZnSO_4 \cdot 7H_2O$ (150 mg) or $Ni(NO_3)_2 \cdot 6H_2O$ (140 mg) and tetraphenylphosphonium chloride (370 mg) is added rapidly to a freshly prepared solution of Cs_2MoOS_3 (470 mg)[9] in H_2O (110 ml).

(4) and *(5)*: An aqueous solution of $Ni(NO_3)_2 \cdot 6H_2O$ (140 mg) or $CoSO_4 \cdot 7H_2O$ (140 mg) and tetraphenylphosphonium chloride (370 mg) is added to a solution of $(NH_4)_2MoO_2S_2$ (230 mg)[10] in H_2O (60 ml).

In each case, the precipitate that is formed is immediately filtered under nitrogen and dried over P_4O_{10} in a vacuum. *(2)* is orange, *(3)* and *(4)* are brown, and *(5)* is green.

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CAS Registry Numbers: *(2)*, 52699-18-0; *(3)*, 52699-20-4; *(4)*, 52699-21-5; *(5)*, 52699-22-6

[1] *A. Müller* and *E. Diemann*, Chem. Commun. *1971*, 65.

[2] *A. Müller, E. Diemann*, and *H.-H. Heinsen*, Chem. Ber. *104*, 975 (1971).

[3] *A. Müller, E. Ahlborn*, and *H.-H. Heinsen*, Z. Anorg. Allg. Chem. *386*, 102 (1971).

[4] *D. E. Peters* and *R. T. M. Fraser*, J. Amer. Chem. Soc. *87*, 2758 (1965).

[5] *C. J. Ballhausen* and *H. B. Gray*, J. Amer. Chem. Soc. *85*, 260 (1963).

[6] *C. K. Jørgensen*, J. Inorg. Nucl. Chem. *24*, 1571 (1962).

[7] *A. B. P. Lever*: Inorganic Electronic Spectroscopy. Elsevier, Amsterdam 1968.

[8] *A. Cormier, K. Nakamoto, E. Ahlborn*, and *A. Müller*, Inorg. Chem., in press.

[9] *A. Müller, E. Diemann*, and *U. Heidborn*, Z. Anorg. Allg. Chem. *371*, 136 (1969).

[10] *G. Krüss*, Liebigs Ann. Chem. *225*, 1 (1884).

4,8-Dioxabicyclo[5.1.0]octa-2,5-diene

By *Helmut Klein* and *Wolfram Grimme*[*]

The rapid reversible Cope rearrangement of bicyclo[5.1.0]octa-2,5-diene (homotropilidene) *(1)*[11] is retarded on replacement of one methylene group by oxygen, but the "fluxional structure" is retained in 8-oxabicyclo[5.1.0]octa-2,5-diene (epoxydihydrotropilidene) *(2)*[12]. It remained to be seen whether replacement of the second methylene group is also tolerated and this dynamic behavior is retained in 4,8-dioxabicyclo-[5.1.0]octa-2,5-diene (epoxydihydrooxepin) *(3)*.

We have synthesized *(3)*, starting with the double epoxidation of 7,7-diethoxynorbornadiene *(4)*[13] with *m*-chloroperbenzoic acid in benzene at room temperature. The *as*-diepoxyacetal *(5)* (70 %; b.p. 63—65 °C/3 × 10^{-3} torr) thus obtained, gave,

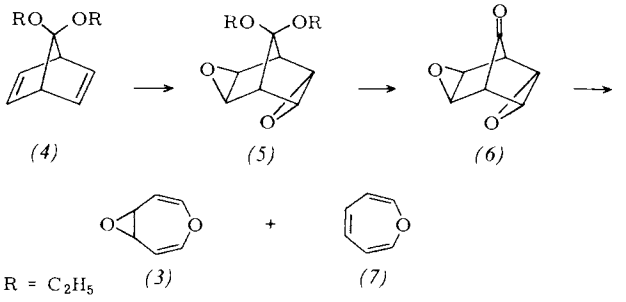
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on hydrolysis in 80% aqueous acetic acid, the corresponding ketone *(6)* [50%; m.p. 142°C, from ethanol; NMR ($CDCl_3$, TMS internal): $\tau = 6.30$ (AA'XX' half spectrum, $J + J' = 4$ Hz)



(1), X = CH_2, Y = CH_2
(2), X = O, Y = CH_2
(3), X = O, Y = O

(epoxide *exo*-H), 6.61 (AA'XX' half spectrum, $J + J' = 3$ Hz) (epoxide *endo*-H), 7.00 ppm (m) (bridgehead-H); IR (KBr): $\nu_{C=O} = 1768\ cm^{-1}$].



(4) *(5)* *(6)* *(3)* *(7)*

R = C_2H_5

On sublimation in a stream of nitrogen (17 ml/min) through a capillary (45 cm, 0.3 cm diameter) heated to 420°C, *(6)* fragments in two ways: the main reaction is the expected decarbonylation leading to 4,8-dioxabicyclo[5.1.0]octa-2,5-diene *(3)* (*ca.* 80%); this is accompanied by formation of oxepin *(7)*[5] (*ca.* 20%) with loss of CO_2. Separation of the products is achieved by dissolving the pyrolyzate in pyridine and converting the oxepin into the Diels-Alder adduct[6] (m.p. 217°C, from ethyl acetate) by addition of *N*-phenylmaleimide. On subsequent distillation (room temperature/10^{-3} torr), *(3)* is collected together with solvent in a receiver cooled to −78°C.

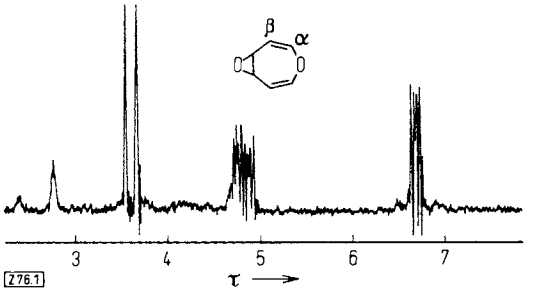
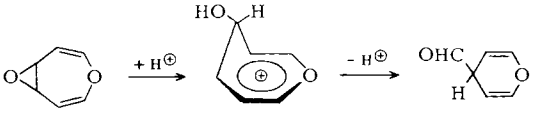


Fig. 1. ^{1}H-NMR spectrum of 4,8-dioxabicyclo[5.1.0]octa-2,5-diene *(3)* (60 MHz, C_5D_5N, TMS internal). The signals at $\tau = 2.38$ and 2.76 ppm are due to the residual ^{1}H of the solvent.

The ^{1}H-NMR spectrum of *(3)* (Fig. 1) contains three groups of signals of equal intensity [(C_5D_5N, TMS internal): $\tau = 3.63$ (d, $J = 7.5$ Hz) (α-olefin H), 4.83 (doubletted AA'XX' half spectrum) (β-olefin H), 6.70 ppm (AA'XX' half spectrum, $J + J' = 6$ Hz) (epoxide-H)]; no line-broading occurs up to 90°C. This clearly indicates that the compound does not undergo a rapid Cope rearrangement, which would render the α-olefin and epoxide protons magnetically equivalent. Loss of "fluxional structure" does not necessarily signify that compound *(3)* is statically present; rather, its mean residence time as one of the two automeric structures at room temperature can be extrapolated to 10^2—10^4 s from the Free enthalpies of activation of *(1)* (14.4 kcal/mol[7]) and *(2)* (*ca.* 17 kcal/mol[2]). The different rates of rearrangement of *(1)* to *(3)* clearly indicate that the cyclic bishomoconjugation in the transition state proceeds more readily *via* methylene bridges than *via* the oxygen bridges. The insulatory effect of the oxygen is not due to any contribution of its lone electron pair in the conjugation—this would lead, in the case of *(2)* to formation of a destabilized $4n$ Hückel system, in the case of *(3)*, however, to a stabilized $(4n + 2)$ Hückel system—but to deformation of its neighboring carbon orbitals *via* which the homoconjugation takes place[8].

As a vinylogous epoxy ether[9] compound *(3)* is sensitive to acids, in the presence of which it rearranges to the 4*H*-pyran-4-carbaldehyde *(9)* [NMR ($CDCl_3$, TMS internal): $\tau = 0.54$ (d, $J = 2.5$ Hz) (aldehyde-H), 3.54 (doublet of triplets) (α-olefin-H), 5.14 (m) (β-olefin-H), 6.44 ppm (m) (tertiary-H)]. The aldehyde *(9)*, which, like its parent compound[10] is unstable towards air, can be catalytically hydrogenated (5% Pd on $CaCO_3$, methanol) to tetrahydropyran-4-carbaldehyde (m.p. 135°C; oxime: m.p. 224°C), which is also readily accessible from tetrahydropyran-4-carboxylic acid[11] by Rosenmund reduction.



(3) *(8)* *(9)*

4,8-Dioxabicyclo[5.1.0]octa-2.5-diene *(3)*, in substance or in benzene solution, immediately rearranges on coming into contact with a glass surface that has not been treated with alkali. The ease and uniformity of rearrangement might best be explained in terms of the homopyrylium ion *(8)* as intermediate.

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CAS Registry Numbers: *(3)*, 52748-31-9; *(4)*, 52748-32-0; *(5)*, 52748-33-1; *(6)*, 52759-93-0; *(9)*, 52748-34-2; tetrahydropyran-4-carbaldehyde, 50675-18-8; tetrahydropyran-4-carbaldehyde oxime, 52748-35-3.

[1] *W. von E. Doering* and *W. R. Roth*, Tetrahedron *19*, 715 (1963).

[2] *H. Klein*, *W. Kursawa*, and *W. Grimme*, Angew. Chem. *85*, 624 (1973); Angew. Chem. internat. Edit. *12*, 580 (1973).

[3] *(4)* is synthesized analogously to the dimethoxy compound [4]; using triethoxymethane for the acetalation of quadricyclanone.

[4] *P. G. Gassman* and *D. S. Patton*, J. Amer. Chem. Soc. *90*, 7276 (1968).

[5] *E. Vogel*, *W. A. Böll*, and *H. Günther*, Tetrahedron Lett. *1965*, 609; *E. Vogel* and *H. Günther*, Angew. Chem. *79*, 429 (1967); Angew. Chem. internat. Edit. *6*, 385 (1967).

[6] *R. Schubart*, Dissertation, Köln 1967.

[7] *H. Günther*, *J. B. Pawliczek*, *J. Ulmen*, and *W. Grimme*, Angew. Chem. *84*, 539 (1972); Angew. Chem. internat. Edit. *11*, 517 (1972).

[8] The $6A_1$-orbital in oxirane illustrates this effect quite clearly: it possesses less "bent-bond" character in the C—C bond than the sym-3E'-orbital (Walsh orbital) of cyclopropane and is antibonding for the C—O bonds; see *W. L Jørgensen* and *L. Salem*: The Organic Chemist's Book of Orbitals. Academic Press, New York 1973, Figures on pp. 154 and 160.

[9] *T. I. Temnikova* and *E. N. Kropacheva*, Zh Obshch. Khim. *19*, 1917 (1949); *C. L. Stevens*, *W. Malik*, and *R. Pratt*, J. Amer. Chem. Soc. *72*, 4758 (1950).

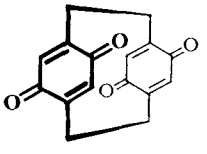
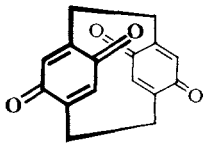
[10] *S. Masamune* and *N. T. Castellucci*, J. Amer. Chem. Soc. *84*, 2452 (1962).

[11] *J. v. Braun* and *Z. Köhler*, Ber. Deut. Chem. Ges. *50*, 1657 (1917); *C. S. Gibson* and *J. D. A. Johnson*, J. Chem. Soc. *1930*, 2525.

[2.2](2,5)Benzoquinonophane: Structure and Photochemistry[1]

By *Hermann Irngartinger, Rolf-Dieter Acker, Walter Rebafka,* and *Heinz A. Staab*[*]

In the context of their investigations on the synthesis of "intramolecular quinhydrones", *Rebafka* and *Staab*[2] recently described two diastereomeric[2.2](2,5)benzoquinonophanes which, on the basis of their syntheses, could be assigned the achiral "pseudogeminal" and chiral "pseudo-ortho" structures *(1)* and *(2)*, respectively. X-ray structure analyses were not only of interest for confirmation of these assignments but also for establishing how the molecular deformation observed in [2.2]paracyclophane[3] is changed on replacing the benzene rings by non-aromatic *p*-benzoquinone moieties, and for examining the differences in the photochemical behavior of *(1)* and *(2)*.

(1)   *(2)*

(1) crystallizes from dioxane in the monoclinic space group $P2_1/n$ with two molecules in the unit cell [$a=7.930(2)$, $b=9.280(2)$, $c=8.024(2)$ Å; $\beta=93.30(2)°$; $d_{calc}=1.51\,g\cdot cm^{-3}$]. For the structure determination, 1440 (incl. 420 "unobserved") reflections were measured by the difference filter method up to $\sin\theta/\lambda=0.66$ on a computer-controlled Siemens single-crystal diffractometer using Mo Kα radiation. The structure could be solved on the basis of 120 *E* (*hkl*) values by direct methods[4] and refined by least squares procedures with inclusion of anisotropic temperature factors for the C and O atoms and isotropic temperature factors for the H atoms. The final *R* value after several cycles was 5.1 %.

The molecule *(1)* (Fig. 1) in the crystal has $\bar{1}$ (C_i) symmetry; deviation from 2/m (C_{2h}) symmetry is essentially due to a parallel shift of the two quinone rings of about 0.24 Å perpendicular to $C^3...C^{6'}$. While the bond lengths and angles within the quinone rings of *(1)* are in good agreement with the values for 2,5-dimethyl-1,4-benzoquinone[5], the $C^7—C^8$ bond, which runs parallel to the repulsive forces within the molecule, is stretched to 1.581 Å. There is also considerable boat-shape deformation of the quinone rings (Fig. 2) due to transannular repulsion. The planes E2 through C^1, C^5 and C^6 and through C^2, C^3 and C^4 are inclined at an average of 16° to the plane E1 through C^1, C^2, C^4 and C^5 (the corresponding deformation in [2.2]paracyclophane is 12.6°[3b]). The carbon-oxygen bonds deviate in opposite directions from E1 by 5.5° ($O^1...O^{2'}$: 3.37 Å). Particularly short distances of 2.73 Å and 3.11 Å are found for $C^3...C^{6'}$ and $C^2...C^{5'}$, *i.e.* for the opposite pairs of carbon-carbon double bonds of the two *p*-benzoquinone systems. Since these double bonds lie parallel to each other in the projection onto E1 (in the plane through them they form an angle of 16.5°), favorable conditions prevail for intramolecular photochemical [2+2]-cycloadditions.

On the other hand, the conditions are particularly unfavorable for an intermolecular photocycloaddition which is normally observed in *p*-benzoquinones: although a center point distance between the $C^2—C^3$ double bond of one molecule and the $C^5—C^6$ double bond of a neighboring molecule is found to be 3.80 Å, *i.e.* shorter than the topochemical maximum distance of 4.2 Å[6], these two double bonds are inclined to each other at an angle of 53.3°.

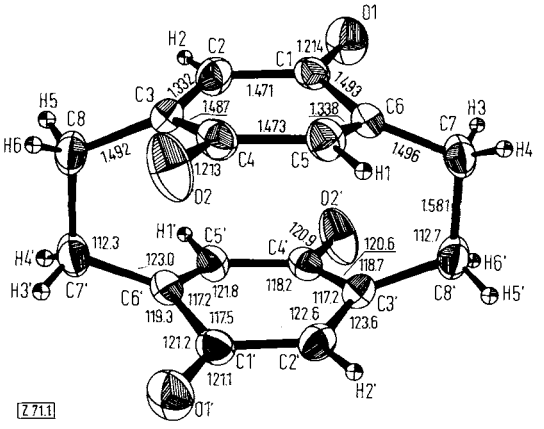


Fig. 1. Bond lengths (Å, standard deviation 0.002 Å) and bond angles (°, standard deviation 0.1—0.2°) of *(1)*, ORTEP drawing: the vibration ellipsoids are drawn at the 50 % probability level for C and O atoms; the H atoms are fixed at 0.1 Å.

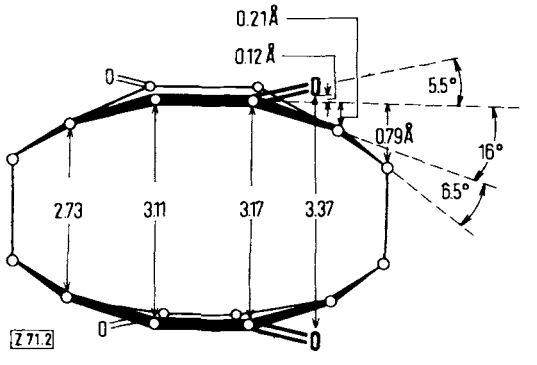
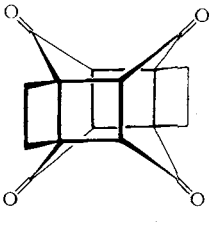


Fig. 2. Transannular distances (Å) and mean deviations from the plane E1 through C^1, C^2, C^4 and C^5 in *(1)*.

Irradiation of *(1)* (900 W Hg high-pressure lamp, Duran filter, 24 h) in the solid state does in fact lead to double intramolecular cycloaddition and formation of a colorless compound (≈90 % yield; dec. >230 °C, from dioxane) having the cage structure *(3)*: ^{1}H-NMR (PFT, 3540 scans, in D_2O): $\delta=2.0—3.6$ (m, 8 methylene-H), 3.76 (s, 4 methine-H); IR: $\nu_{C=O}=1710\,cm^{-1}$ (in dioxane); UV: no maximum above 200 nm; MS: M^+ calc. for $C_{16}H_{12}O_4$ 268.0734, obs. 268.0736. Typical of the mass spectrometric fragmentation is the successive cleavage of the four carbonyl groups down to $C_{12}H_{12}$ and the corresponding cleavage in the (M−1H) series; other important fragment ions are $m/e=214$ (80 %), 201 (100 %), 115 (43 %). Similarly to the structurally related cage compounds obtained by photodimerization of dimethylbenzoquinones[7], compound *(1)* takes up water to give a dihydrate.

 *(3)*

As expected, in contrast to *(1)* no intramolecular cycloaddition of the *p*-benzoquinone units can be observed on irradiation of diastereomeric *(2)* under the same conditions or for longer radiation times. Rather, a considerably slower intermolecular photoreaction takes place to give a high molecular weight

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product (40 % yield after 73 h). A topochemical interpretation of this photoreaction is not yet possible, since changes are also observed during collection of the X-ray data of *(2)* [$a = 9.09$, $b = 23.65$, $c = 11.44$ Å; $\beta = 90.9°$; space groups: $P2_1/c$, $Z = 8$; $D_{calc.} = 1.45$].

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German version: Angew. Chem. 86, 705 (1974)

CAS Registry Numbers: *(1)*, 52729-66-5; *(2)*, 50874-32-3; *(3)*, 52571-23-0.

[1] Transannular interactions in [2.2]phanes, Part 7. Part 6: *M. Haenel*, Tetrahedron Lett., *1974*, 3053.

[2] *W. Rebafka* and *H. A. Staab*, Angew. Chem. *85*, 831 (1973); *86*, 234 (1974); Angew. Chem. internat. Edit. *12*, 776 (1973); *13*, 203 (1974).

[3] a) *C. J. Brown*, J. Chem. Soc. *1953*, 3265; b) *H. Hope*, *J. Bernstein*, and *K. N. Trueblood*, Acta Crystallogr. *B 28*, 1733 (1972).

[4] LSAM program by *G. Germain*, *P. Main*, and *M. M. Woolfson*, Acta Crystallogr. *A 27*, 368 (1971).

[5] *D. Rabinovich* and *G. M. J. Schmidt*, J. Chem. Soc. *1964*, 2030.

[6] *G. M. J. Schmidt*, J. Chem. Soc. *1964*, 2014; Pure Appl. Chem. *27*, 647 (1971).

[7] *R. C. Cookson*, *D. A. Cox*, and *J. Hudec*, J. Chem. Soc. *1961*, 4499; see also *H. Hopf* and *H. Musso*, Chem. Ber. *106*, 143 (1973).

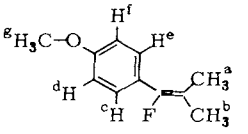
Reaction of a Vinyl Fluoride with Antimony Pentafluoride. Spectroscopic Evidence for a Stable Vinyl Cation[1][**]

By *Hans-Ullrich Siehl*, *James C. Carnahan Jr.*, *Lothar Eckes*, and *Michael Hanack*[*]

Vinyl cations have been shown to be reactive intermediates in many solvolytic, addition, and rearrangement reactions[2]. However, all previous attempts to produce and spectroscopically detect long-lived vinyl cations have so far failed[3].

In the present communication we report the first attempt to apply the methods formerly used for the generation of trisubstituted carbenium ions[4] to the reaction of vinyl halides and to record the ^{1}H- and ^{13}C-NMR spectra of the resulting solutions at low temperatures.

Table 1. ^{1}H-NMR spectrum of *(1)* in CCl_4 at 22 °C, and of [*(1)* + SbF_5] in SO_2ClF at −73 °C. Chemical shifts in ppm from external TMS = 0.



(1)

	(1)		[*(1)* + SbF_5]	
H^a	1.73	$J_{H^a-F} = 3.4$ Hz	2.22	
H^b	1.80	$J_{H^b-F} = 2.9$ Hz	2.22	
H^c	7.24	$J_{c-d} = 8.3$ Hz	8.58	$J_{c,d}$ ca. 9 Hz
H^d	6.78		7.41	$J_{c,f}$ ca. 10 Hz
H^e	7.24		8.82	
H^f	6.78		7.57	
H^g	3.74		4.50	

In a typical experiment, very small droplets of a cooled solution of 1-fluoro-1-(*p*-methoxyphenyl)-2-methyl-1-propene *(1)* (1.5 mmol) in SO_2ClF (2 ml) was added under nitrogen and with vigorous stirring to a cooled (−78 °C) solution of purified SbF_5 (17 mmol) in SO_2ClF (2 ml)[5]. The reddish homogeneous solution was transferred under nitrogen to a cooled NMR

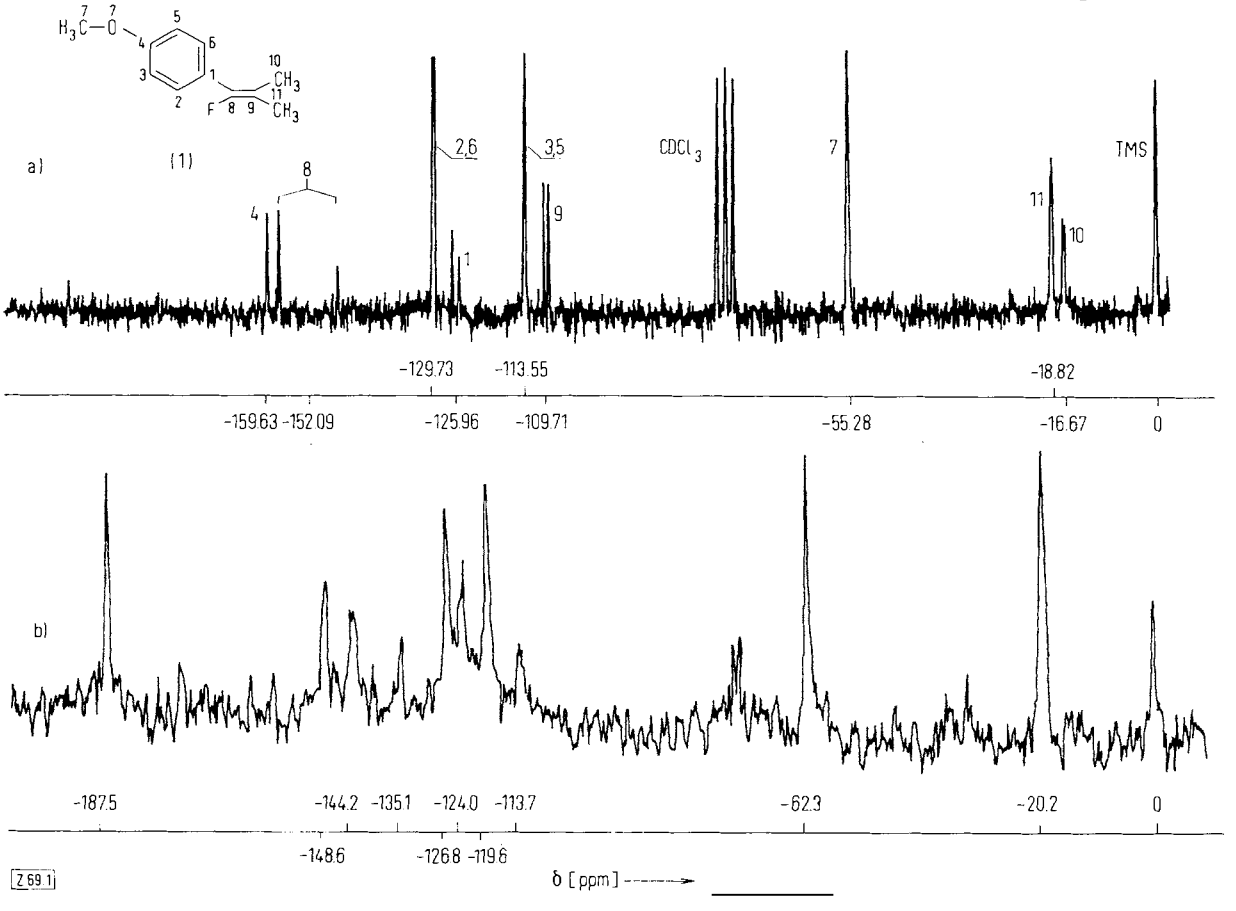


Fig. 1. a) FT ^{13}C-NMR spectrum of *(1)* (proton broad-band decoupled, TMS = 0 ppm) in $CDCl_3$ at 22 °C. Coupling constants: $J_{C_1-F} = 30.9$, $J_{C_{2,6}-F} = 4.4$, $J_{C_8-F} = 236.8$, $J_{C_9-F} = 20.6$, $J_{C_{10}-F} = 9.6$, $J_{C_{11}-F} = 4.4$ Hz. b) FT ^{13}C-NMR spectrum of *(1)* SbF_5 (proton broad-band decoupled, ext. TMS = 0 ppm) in SO_2ClF at −50 °C.

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[**] This work was supported by the Fonds der Chemischen Industrie and the Deutsche Förschungsgemeinschaft. We thank Prof. *G. Olah* for helpful discussions on the interpretation of the spectra.

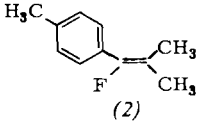
tube[5] and frozen in liquid nitrogen until the spectra were recorded.

In contrast to the ^{1}H-NMR spectrum of *(1)*, that of the reaction product of *(1)* with SbF_5 $[(1) + SbF_5]$ shows downfield shifts (Table 1). At -73 °C the aromatic region of the spectrum of $[(1) + SbF_5]$ is similar to that of the *p*-methoxybenzyl cation investigated under the same conditions by *Olah*[6], as regards both the chemical shift of the protons as well as the non-equivalence of the two *o*- and *m*-protons (H^c, H^e and H^d, H^f, respectively).

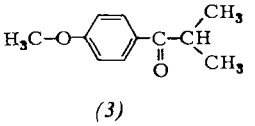
Figure 1 shows the ^{13}C-NMR spectra of *(1)* (Fig. 1a) and $[(1) + SbF_5]$ (Fig. 1b). In the spectrum of $[(1) + SbF_5]$ the methyl groups (C^{10}, C^{11}) that are shifted only slightly downfield appear as a single signal. The C—F couplings are no longer visible. An especially large downfield shift is observed in the case of the signal at 187.5 ppm, which according to the "off-resonance" spectrum corresponds to a quaternary C atom. This signal can be assigned to C^4, since it is shifted downfield by about the same amount as the corresponding signal in the spectrum of the *p*-methoxybenzyl cation[6]. In the "off-resonance" spectrum, the signals at 148.6 and 144.2 ppm and 126.8 and 119.6 ppm, respectively, form doublets and can analogously be assigned to the *ortho* (C^2, C^6) and *meta* (C^3, C^5) positions. The non-equivalence of C^2 and C^6 and of C^3 and C^5 is presumably due to the frozen rotation of the CH_3O group at low temperatures[6]. The assignment of the signals should be regarded as tentative.

That the two methyl C atoms (C^{10}, C^{11}) in $[(1) + SbF_5]$ give rise to only one signal is consistent with the expected symmetry of a substituted linear vinyl cation. A complexation of *(1)* with SbF_5 at the *p*-methoxy group can be ruled out as the sole cause of the observed downfield shift by comparison of the spectra of *(1)* and *(2)* with SbF_5. Protonation of *(1)* and *(2)* with HSO_3F/SbF_5 (1:1) produced the spectroscopically identified aryl(fluoro)isopropylcarbenium ions.

Preliminary ^{13}C-NMR measurements on *(1)* with specific ^{13}C-enrichment at the functional C-atom (C^8)[7] show two intense signals at 174.9 and 189.7 ppm in SbF_5/SO_2ClF. Consequently, the presence of a second species or occurrence of an exchange process cannot yet be ruled out with certainty. All ^{13}C-NMR spectra of $[(1) + SbF_5]$ were accurately reproducible to at least 0.9 ppm.



(2)



(3)

A solution of $[(1) + SbF_5]$ (with specifically ^{13}C-enriched *(1)*) in SO_2ClF was added dropwise to a cooled suspension of K_2CO_3 in methanol and (after work-up with pentane) investigated by gas-chromatography. The sole product found was the ketone *(3)*, which, after isolation, was identified by its NMR, IR and mass spectra[8]. The absolute yield of ketone *(3)* ranged between 20 and 40%; the fluoride *(1)* is stable under the experimental conditions used. Quantitative mass spectrometric investigations on *(3)* showed no changes in the position of the labeled C atom.

Within the limits mentioned above, we interpret the spectroscopic data reported here as the first evidence for the occurrence of a stable long-lived vinyl cation in the reaction of a vinyl halide with antimony pentafluoride. This is supported by the observed downfields shifts of the ^{1}H and ^{13}C-NMR signals, and especially by the similarity between the spectrum of $[(1) + SbF_5]$ and that of the *p*-methoxybenzyl cation regarding the signals in the aromatic region and the shift of the methoxy group.

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CAS Registry Numbers: *(1)*, 52571-00-3; $[(1) + SbF_5]$, 52571-01-4; SbF_5, 7783-70-2.

[1] Vinyl Cations, Part 18.—Part 17: *H. Stutz* and *M. Hanack*, Tetrahedron Lett. *1974*, 2457.

[2] *K. P. Jäckel* and *M. Hanack*, Tetrahedron Lett. *1974*, 1637, and literature cited therein.

[3] Cf. *G. A. Olah, Y. K. Mo*, and *Y. Halpern*, J. Org. Chem. *37*, 1169 (1972); cf. also *Ch. U. Pittmann jr.* and *G. A. Olah*, J. Amer. Chem. Soc. *87*, 5632 (1965); *H. G. Richey jr., J. C. Philips*, and *L. E. Rennick*, *ibid.* *87*, 1381 (1965).

[4] *G. A. Olah*, Angew. Chem. *85*, 183 (1973); Angew. Chem. internat. Edit. *12*, 173 (1973).

[5] For a description of the equipment see *M. Hanack et al.*, unpublished.

[6] *G. A. Olah, R. D. Porter, C. L. Jeuel*, and *A. M. White*, J. Amer. Chem. Soc. *94*, 2044 (1972). The ^{1}H- and ^{13}C-NMR spectra obtained for the *p*-methoxybenzyl cation under the conditions used by us were the same as those obtained by *Olah et al.*

[7] *J. Salaun* and *M. Hanack*, unpublished results.

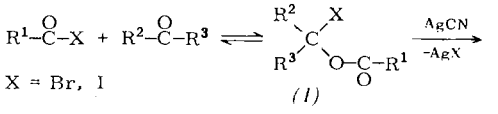
[8] *I. Inukai* and *R. Yoshizawa*, J. Org. Chem. *32*, 404 (1967).

α-Acyloxy Isocyanides ("*O*-Acyl Isocyanohydrins")

By *Gerhard Höfle*[*]

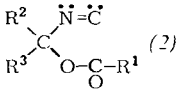
While the formation and transformation of the cyanohydrins have been investigated in detail, to our knowledge no reference has as yet been made to isomers with the isocyanide structure. In the present communication we report on the *O*-acyl derivatives of this type of compound.

Thus, reaction of benzoyl bromide with silver cyanide in acetone leads to formation of α-benzoyloxy isocyanide *(2a)* (1-isocyano-1-methylethyl benzoate) and no trimeric benzoyl isocyanide[1, 2]. The structure of *(2a)* follows unambiguously from the spectroscopic data (cf. Table 2). Presumably the α-acyloxy bromide *(1a)*, which is present in low equilibrium concentration along with acyl bromide and ketone[3], reacts according to a classical isocyanide synthesis more rapidly than acyl bromide with silver cyanide.



X = Br, I

(1)



(2)

As expected, the isolable α-acyloxy bromides *(1c)* and *(1d)*[5] also afford the isocyanides *(2c)* and *(2d)* in high yields. Experiments have shown that the S_N1 reactivity of *(1)* plays a decisive role in the reaction. Despite the levelling influence of the acyloxy group, it depends strongly on the nature of the α-substituents R^2 and R^3 and the leaving group X. Thus, in the case of R^2, R^3 = alkyl and R^2 = phenyl, R^3 = H, the

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bromide affords the best results, while in the case of R^2 = alkyl, R^3 = H the iodide is to be preferred[4]. *(1f)* also reacts only slowly with X = iodine[4]. No reaction takes place in the case of the chlorides *(1)*.

An overview of the isocyanides *(2)* prepared, and their characteristic spectroscopic data, is presented in Tables 1 and 2. The compounds are colorless crystals or liquids, which become dark and resinous at room temperature and in the presence of air.

The isocyanides *(2)* are relatively stable toward alkaline hydrolysis; thus, in their isolation, removal of silver salts[7] is accomplished by shaking with *ca.* 20% potassium cyanide solution. On the other hand, momentary hydrolysis takes place in 1 N HCl/acetone to give carbonyl compounds, hydrogen cyanide, and carboxylic acids, and, in the case of *(2c)*, smaller amounts of *N*-(α-hydroxybenzyl)formamide. Whether acid hydrolysis proceeds *via* the isocyanohydrin, has still to be investigated.

Table 1. Isocyanides *(2)* prepared [6].

	R^1	R^2	R^3	X	Method [a]	Yield [%] [b]	B.p. [°C/torr]	M.p. [°C]
(2a)	C_6H_5	CH_3	CH_3	Br	A	85(95)	86/0.05	37
(2b)	CH_3	$-(CH_2)_4-$		Br	A	59(76)	53/0.1	
(2c)	$C(CH_3)_3$	H	C_6H_5	Br	B	72(93)	140/0.1 [c]	
(2d)	CH_3	H	$2,4\text{-}(CH_3COO)_2C_6H_3$	Br	B	92		86–88
(2e)	C_6H_5	CH_3	H	I	C	79	120/0.1 [c]	12–13
(2f)	C_6H_5	H	H	I	C	67	120/0.1 [c]	

[a] See experimental.
[b] The values in brackets refer to NMR spectroscopically pure products after removal of solvent in a high vacuum.
[c] Furnace-temperature in bulb tube distillation.

Table 2. Characteristic IR, ^{1}H-NMR and ^{13}C-NMR spectroscopic data of the isocyanides *(2a)*, *(2c)*, *(2e)* and *(2f)*.

	IR (CCl_4) [cm^{-1}]	^{1}H-NMR (in CCl_4, TMS = 0) δ [ppm]	^{13}C-NMR (in $CDCl_3$, TMS = 0) δ [ppm] C—N=C	
(2a)	2130; 1748	1.96 (6H, s)	85.4	159.9
(2c)	2130; 1759	1.27 (9H, s); 6.92 (1H, s)	75.6	162.3
			$J_{HCN^{13}C}$ = 2.5 Hz	
(2e)	2140; 1750	1.74 (3H, d), J = 6 Hz; 6.17 (2H, q), J = 6 Hz	72.7	161.2 [a]
(2f)	2152; 1752	5.4 (2H, s)	63.6	163.3 [a]

[a] $J_{HCN^{13}C}$ is not determined.

Experimental:

Method A: Acyl bromide (20 mmol) is added with cooling to a stirred suspension of silver cyanide (22 mmol) in ketone (0.2 mol). After 30 minutes the ice-bath is removed and stirring is continued for a further 3—5 h. The excess of ketone is then removed by evaporation in a vacuum and chloroform and 20% potassium cyanide solution are added until all salts are dissolved. The organic phase is dried over $MgSO_4$ and the solvent evaporated off in a vacuum. The residue is distilled or recrystallized from petroleum ether.

Method B: α-Acyloxy bromide *(1)*[5] (20 mmol) is added to a suspension of silver cyanide (42 mmol) in chloroform (30 ml). After 3—5 hour's stirring, the same procedure as in Method A is followed.

Method C: α-Acyloxy iodide *(1)*[4] (20 mmol) is added to a suspension of silver cyanide (44 mmol) in chloroform (20 ml) and stirred, in the case of *(2e)* for 1—2 h, in the case of *(2f)* for 24 h. Thereafter the same method as in A and B is followed.

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revised: July 11, 1974
German version: Angew. Chem. *86*, 679 (1974)

CAS Registry Numbers: *(1c)*, 52571-14-9; *(1d)*, 52571-15-0; *(1e)*, 52571-16-1; *(1f)*, 13943-33-4; *(2a)*, 52571-17-2; *(2b)*, 52571-18-3; *(2c)*, 52571-19-4; *(2d)*, 52571-20-7; *(2e)*, 52571-21-8; *(2f)*, 52571-22-9; benzoyl bromide, 618-32-6; acetyl bromide, 506-96-7; acetone, 67-64-1; cyclopentanone, 120-92-3; silver cyanide, 506-64-9.

[1] *J. U. Nef*, Liebigs Ann. Chem. *287*, 303 (1895); *H. Dounchis*, J. Org. Chem. *37*, 2583 (1972); *G. Höfle*, Tetrahedron Lett. *1974*, 347.

[2] Thanks are due to Professor *H. A. Staab* for drawing our attention to the publication by *H. Dounchis*.

[3] Mixtures of benzoyl bromide and acetone do not show any new signals in the NMR spectrum; independently prepared iodide *(1a)* decomposes at room temperature into benzoyl iodide and acetone [4].

[4] *G. Wittig* and *M. Jautelat*, Liebigs Ann. Chem. *702*, 24 (1967).

[5] The bromides *(1c)* and *(1d)* are formed quantitatively if the corresponding benzaldehyde is mixed with 2—3 mol acyl bromide and the excess of the latter is removed by distillation under vacuum at room temperature immediately before further use.

[6] All compounds gave correct elemental analyses.

[7] The silver can be recovered quantitatively from the aqueous solution by reduction with zinc dust.

Reviews

Abstracts of selected progress reports and review articles

Applications of X-ray photoelectron spectroscopy (ESCA) in inorganic chemistry are discussed in a review by *W. L. Jolly*. The main value of this method for chemists lies in the fact that core electron binding energies are a function of the chemical environment of the atoms, *i.e.* they are subject to a "chemical shift". This chemical shift is correlated with atomic charge. Thus, it is possible to identify oxidation states, even if they are non-integral. This is important for the proof of valence electron delocalization, especially in coordination compounds. Similarly, π back-bonding, pπ→dπ bonding, and ligand structure and orientation can be investigated with the aid of this method. [The Application of X-Ray Photoelectron Spectroscopy to Inorganic Chemistry. Coord. Chem. Rev. *13*, 47—81 (1974); 119 references]

[Rd 722 IE—H]

The synthesis of carbocyclic spiro compounds containing skeletal units such as *(1)* ***via* intramolecular alkylation routes** is reviewed in an article by *A. P. Krapcho*. There are six different types of reaction: 1) Intramolecular dehydrohalogenations, dehydrotosylations, and related reactions *e.g.* the cyclization of 2-(ω-bromoalkyl)cycloalkanones and 9-(ω-haloalkyl)fluorenes and the intramolecular dehydration of 2-(2-hydroxyethyl)-cyclohexanones lead to *(1)*. 2) Di- and tetraalkylations of ketones with α,ω-dihaloalkanes and subsequent dehalogenation yields spiroketones in one step; dispiro- and polyspiroketones can also be synthesized in this way. The reaction of

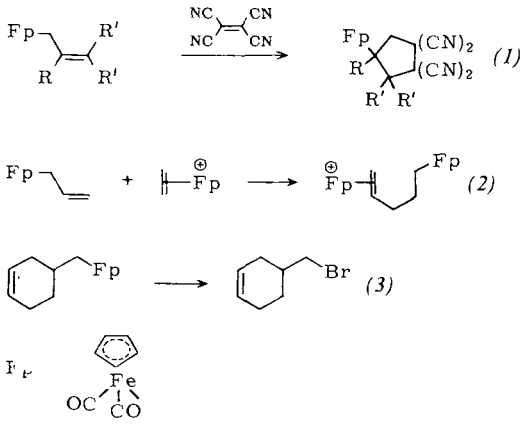


(1)

malonic esters with α,ω-dihaloalkanes, and especially with ditosylates, permits formation of spiro- and polyspiro-linkages. 3) Reductive intramolecular dehalogenation leads to spiropentanes and spirocyclopropane systems and their ketones. 4) Free radical cyclization, such as oxidative coupling of phenol to double bonds and photochemical dehydrobrominations also yield *(1)*. 5) Acid-catalyzed cyclizations (cyclodehydration of alcohols with suitably placed double bond or aromatic ring, cyclization of *ene-ene* or *ene*-aromatic systems) open up further synthetic routes. 6) Thermal cyclizations which yield *(1)* are, *e.g.*, those of cyclic ketones containing a 1-butenyl residue. The thermal or photochemical decomposition of spiropyrazoline adducts (addition of diazo compounds to unsaturated substrates) permit the synthesis of further compounds *(1)*. [Synthesis of Carbocyclic Spiro Compounds *via* Intramolecular Alkylation Routes. Synthesis *1974*, 383—419; 372 references]

[Rd 723 IE—M]

Organoiron complexes as potential reagents in organic synthesis is the title of a paper by *M. Rosenblum*. A simple example for a metal-assisted [3+2]-cycloaddition is the reaction of σ-allyl derivatives of dicarbonyl(η-cyclopentadienyl)iron with tetracyanoethylene to give the cyclopentane derivatives of type *(1)*. With cyclic allyl compound, bicyclenes are obtained. Such cycloaddition reaction may also be effected *e.g.* with

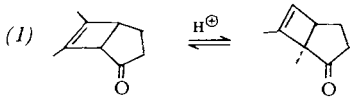


(1) *(2)* *(3)*

the corresponding propargyl-, allenyl-, and cyclopropylmethyl complexes. Other sections of the review are devoted to the synthesis of cationic dicarbonyl(η-cyclopentadienyl)iron-olefin complexes, their reactions with nucleophiles, organometal condensations, *e.g.* to give *(2)*, and demetalation, *e.g.* to give *(3)*. [Organoiron Complexes as Potential Reagents in Organic Synthesis. Accounts Chem. Res. 7, 122—128 (1974); 45 references]

[Rd 724 IE—L]

Acid-catalyzed rearrangements of β,γ-unsaturated ketones, especially in molecules with high ring strain, are reviewed in an article by *R. L. Cargill, T. E. Jackson, N. P. Peet,* and *D. M. Pond*. An example is the almost quantitative isomerization *(1)*→*(2)*. Electron donation from the double bond to the electron deficient carbonyl carbon is the first step

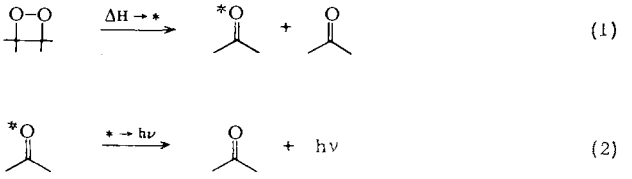


(1)

of the reaction (after protonation of the carbonyl carbon). Usually either 1,3-acyl or 1,2-vinyl shifts are encountered. Numerous applications are forseen for these rearrangements in syntheses. [Acid-Catalyzed Rearrangements of β,γ-Unsaturated Ketones. Accounts. Chem. Res. 7, 106—113 (1974); 49 references]

[Rd 725 IE—L]

Tetramethyl-1,2-dioxetane *(1)*, and its use in chemiexcitation, chemiluminescence, photochemistry, chemical dynamics, and spectroscopy are reported on by *N. J. Turro, P. Lechtken, N. E. Schore, G. Schuster, H-Ch. Steinmetzer,* and *A. Yetka*. *(1)* can serve as a source of excited acetone molecules. Its



(1)

(2)

suitability for fundamental investigations in the fields quoted stems from the appropriate coupling of the high selectivity of the chemiexcitation step [Eq. (1)] with the experimental

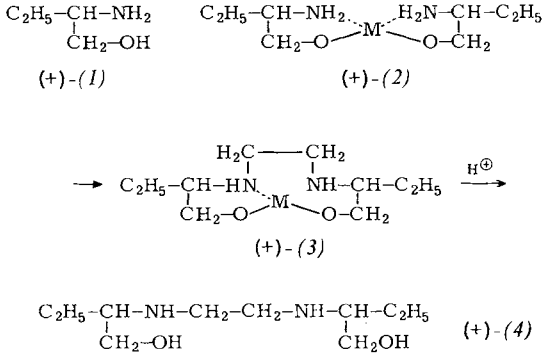
simplicity and sensitivity of the luminescence step [Eq. (2)]. [Tetramethyl-1,2-dioxetane. Experiments in Chemiexcitation, Chemiluminescence, Photochemistry, Chemical Dynamics, and Spectroscopy. Accounts Chem. Res. 7, 97—105 (1974); 38 references]

[Rd 726 IE—L]

Patents

Abstracts of selected "Deutsche Offenlegungsschriften" (DOS), *i. e.* provisionally published specifications as filed with the German Patent Office

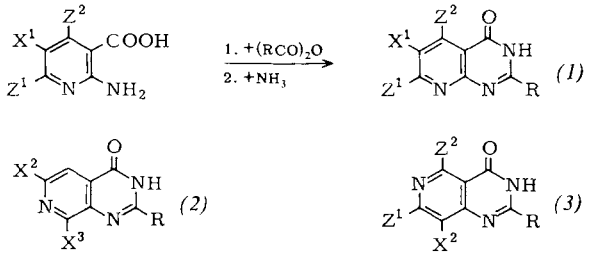
An improved process for the preparation of the tuberculostatically active (+)-2,2'-(ethylenediimino)-di-1-butanol *(4)* proceeds *via* the complex salts *(2)*. These react with 1,2-dihaloethane to form the complexes *(3)*, from which the salts of *(4)*



are liberated by acids; this procedure gives lower yields of by-products and isomers (M = Cu^{II}, Ca). [DOS 2328035; Mitsui Toatsu Chemicals Inc.; Mitsui Pharmaceuticals, Inc., Tokyo (Japan)]

[PR 210 IE—K]

2-Substituted pyrido[2,3-*d*]- *(1)* -[3,4-*d*]- *(2)* and [4,3-*d*]pyrimidine -4(3*H*)-one *(3)*, especially the compounds *(1)*, comprise a new class of herbicidally active substances which can be used both before and after the germination period. The com-

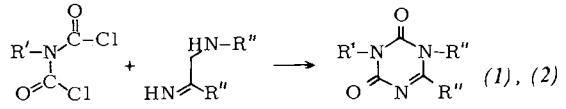


R = Alkyl (C_3—C_5), Cycloalkyl, C_1—C_2-Polyfluoro(chloro)-alkyl; X^1 = H, Cl, Br, Alkyl; X^2, X^3 = H, Cl, Br; Z^1, Z^2 = H, CH_3

pounds can be prepared not only from the acid form (+ NH_3) but also from the amide (+ $OH^{\ominus}$) and the nitrile (+ $H_2O_2/OH^{\ominus}$). [DOS 2348111; Pfizer Inc., New York (USA)]

[PR 212 IE—S]

Powerful photosynthesis inhibitors suitable for use as weedkillers: the new 1,2,5-triazine-2,4(1*H*,3*H*)diones of formula *(1)* and especially *(2)*. The preferred method of preparation is by the reaction of bis(chlorocarbonyl) amines with *S*-alkyl-

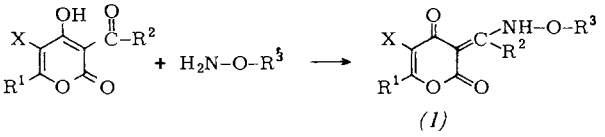


(1): R' = alkyl, cycloalkyl, aralkyl, aryl; R'' = H, alkyl, cycloalkyl, aralkyl, aryl, OH, OAlk, NR_2; R''' = *(inter alia)* H, alkyl, Hal, OAlk, SAlk, NR_2
(2): R'' = NH_2; R''' = SCH_3, NH_2, $N(CH_3)_2$

isothiuronium compounds or guanidines, amidines, *etc.* [DOS 2254200; Bayer AG Leverkusen]

[PR 213 IE—S]

3-(*N*-Alkoxyaminoalkylidene)pyran-2,4-diones, of formula *(1)*, which can be prepared by the reaction of 4-hydroxy-3-acyl-α-pyrones with *O*-alkylhydroxylamines, are a new type of herbi-



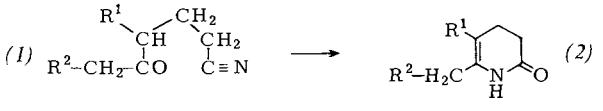
(1)

X = H, halogen; R^1 = alkyl, phenyl; R^2 = alkyl, nitrophenyl, benzyl, phenoxymethyl; R^3 = H, alkyl, alkenyl, alkynyl, benzyl

cides acting specifically on graminaceous weeds. [DOS 2352661; Nippon Soda Co. Ltd., Tokyo (Japan)]

[PR 214 IE—S]

Unsaturated γ-lactams *(2)* are obtained by heating α-cyanoethylated ketones *(1)* in the presence of aqueous sulfuric

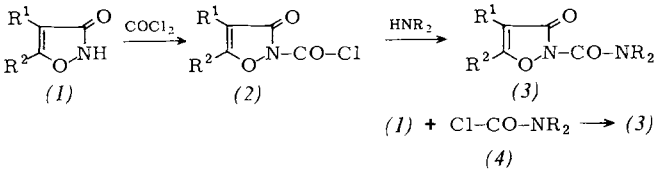


R^1, R^2 = H, Alkyl

acid. [DOS 2245097; Deutsche Texaco AG, Hamburg]

[PR 217 IE—K]

Isoxazolinone derivatives *(3)* with analgesic, anti-inflammatory, and other pharmacological properties are formed from isoxazolinones *(1)* by reaction with phosgene and subsequent replacement of the chlorine by an amino group or from *(1)*



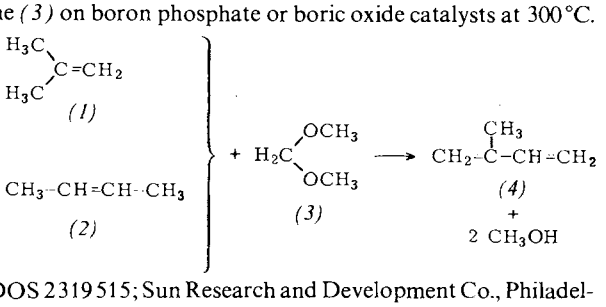
(1) + Cl-CO-NR_2 → *(3)*
(4)

R^1 = H, alkyl, halogen; R^2 = H, alkyl, aryl, alkoxycarbonyl; NR_2 = saturated cyclic amine

and an *N*-chlorocarbonyl-substituted saturated cyclic amine *(4)*. [DOS 2257750; Sankyo Co. Ltd., Tokyo (Japan)]

[PR 218 IE—K]

Isoprene *(4)* is obtained in good yield in a single-step reaction from isobutene *(1)* and/or but-2-ene *(2)* with dimethoxymethane *(3)* on boron phosphate or boric oxide catalysts at 300 °C.



[DOS 2319515; Sun Research and Development Co., Philadelphia (USA)]

[PR 219 IE—G]

Entropy. The Devil on the Pillion. A Popular Exposition. By *J. Zernike*. Kluwer, Deventer 1972, 1st Edit., 150 pp., numerous figures, bound hfl. 34.75.

The title of this book can lead to misunderstandings: apart from the *Maxwell* and *Arrhenius* demons, which in the last chapter are taken to absurdity, everything is very down-to-earth and reasonable. It is doubtful whether the consistent omission of differential derivatives and integrals will prove popular, no matter how skilfully done, for a follower of the creed that school mathematics are the work of the devil will hardly have the ambition to achieve statistical understanding of thermodynamics.

The book offers some valuable advantages. In the first chapter the author presents a very interesting history of the development of thermodynamics without succumbing to the obvious temptation of using unclear expressions. Unfortunately, the history of thermodynamics as a didactic method has been rather overlooked, an unjustifiable trend as *Zernike* shows.

The avoidance of differential and integral calculus necessitates, in the second chapter, derivation of the Clausius-Clapeyron equation by a cycle. Nevertheless, the term "function of state" is explained.

Chapters 3 and 4 are the best part of the book because they contain at last statistical thermodynamics which any chemist can understand. This fills a sorely-felt gap, for in otherwise good thermodynamics textbooks a more than primitive statistical treatment of entropy is usually missing.

The last two chapters are merely an appendage. *Auerbach*'s "ectropism" and *Arrhenius*' demon were wrong approaches and present an unnecessary burden for the reader. Instead the author could have made better use of his didactic skill by presenting some modern developments in irreversible thermodynamics, as the works of *Prigogine*, *Glansdorff*, *Monod*, and *Eigen* permit a less defeatist opposition to the philosophers' criticism of the concept of a heat death of the Universe.

Arno Höpfner [NB 215 IE]

Identification and Analysis of Plastics. By *J. Haslam*, *H. Willis*, and *D. Squirrell*. Butterworth, London 1972. 2nd ed., 748 pp., numerous figures, bound £ 18.00.

Among the more recent guides to the analysis of plastics this book deserves a special place, as it treats together both qualitative and quantitative procedures with chemical and physical methods.

The first part deals with instrumental methods such as UV, IR, NMR, and gas chromatography (including pyrolysis), the methods being illustrated with some practical examples. Then follows qualitative analysis, not only by simple chemical tests, but also by appropriate physical techniques. Subsequent chapters are devoted to vinyl polymers, polyesters, polyamides, polyolefins, fluorinated plastics, rubber-like materials, thermosetting resins, and natural polymers like cellulose and some other classes of plastics. The last part presents details of the analysis of plasticizers, fillers, and solvents. Finally, the book contains a collection of IR spectra of important plastics, although their number and quality of reproduction cannot be compared with the well-known tables by *Hummel*.

For expert analysts the book presents a plentiful source of valuable information from the authors' practical experience; this will undoubtedly be its principal use. The beginner may be overwhelmed by the abundance of material, especially as the layout is not at all clear and the index covers only the 11 main chapters. The next edition really must be more clearly subdivided, so that the reader can find what he needs more rapidly and is not limited to the short index. About 350 bibliographic citations supplement the work, but these have been chosen rather arbitrarily; they usually refer to the authors' own work and are largely limited to publications in English. Thus, the book is a valuable collection of information but it does not always come up to its ambitious title. Any new edition should introduce a more rigorous arrangement of subject matter and a more careful selection of the many methods and details.

Dietrich Braun [NB 217 IE]

Deuterium Labeling in Organic Chemistry. By *A. F. Thomas*. Appleton-Century-Crofts Educational Div./Meredith Corp., New York 1972. 1st edit., xiii, 518 pp., numerous figures, bound, DM 101.80.

Hydrogen atoms in the "stable" bonds of organic compounds are frequently responsible for much more than we are normally aware of or consider. It is therefore far from easy to prepare a compound deuterated in a specific position. The author is well aware of this and has written a truly useful book, but deuterium labeling and its application range into so many specialized fields that the subject is almost too taxing for a single author. It is not surprising, therefore, that chapters which do not deal with the preparative aspect are not entirely satisfactory and that some of the propositions are not quite correct. To mention but two examples: there is no negative isotope effect (p. 38), and an starved yeast is quite different from a denatured yeast (p. 424).

Eight chapters of the book deal with methods of deuteration. The classification is based on the mechanisms and processes which lead to the compounds. These chapters contain an abundance of interesting chemistry. One chapter is devoted to biochemical deuteration, but the many possibilities of stereospecific deuteration are insufficiently appreciated. Another chapter finally deals with isotope effects and analytical procedures. A list 33 pages long of molecular formulas of deuterated compounds, with a brief outline of the method of preparation, is really useful. What makes this book, which contains almost 2000 references, particularly valuable and worthy of recommendation is that the author has the courage and the necessary experience to make critical evaluations. He draws attention to the advantages and weaknesses of individual methods, and gives many practical guidelines.

Helmut Simon [NB 222 IE]

Grundlagen der Stereochemie (Elements of Stereochemistry). By *E. L. Eliel*. UTB, Verlag Birkhäuser Basel—Stuttgart 1972. 108 pp., numerous figures, bound, DM 9.80.

A chemist who has left University ten years ago frequently finds difficulty in reading recent articles on stereochemistry. He encounters many concepts which were never raised during his studies, and many of the notations have acquired different meanings. This is due to the fact that during the last few years stereochemistry has undergone drastic changes with regard to problem formulation, applied experimental methods, and conceptual definition and classification of stereochemical phenomena.

This book will assist those for whom the transition from the earlier, mainly experimentally oriented mode of thinking to the current, more abstract approach is too abrupt.

The didactic arrangement and flowing style make the book a pleasure to read. The descriptions of experimental results and the theoretical discussion are well balanced. Even the untrained reader will find little difficulty in understanding the material and will not have to resort to additional reading (only in the application of the Cahn-Ingold-Prelog rules to multiple bond systems would some additional remarks have been useful). Exercises (with answers) round off the positive impression made by the book.

The book is recommended not only to all students after their preliminary examinations but to all who want to brush up their knowledge and would like a readable introduction to modern stereochemistry.

Günther Maier [NB 224 IE]

Comprehensive Chemical Kinetics. Vol. 4. Decomposition of Inorganic and Organometallic Compounds. By *C. H. Bamford* and *C. F. Tipper*. Elsevier Publishing Company, Amsterdam—London—New York 1972. 1st edit., xii, 272 pp., numerous figures and tables, bound, $ 27.25.

This volume, together with volume 5, constitutes Section 2 "Homogeneous Decomposition and Isomerization Reactions" of the above work. As suggested by the title, all those reactions are discussed which proceed, if not necessarily unimolecularly, at least in the absence of a foreign reactant. Major attention is always paid to the primary reaction (in the true sense), and secondary reactions between reactant molecules and decomposition products are in general only dealt with when they have been shown to contribute significantly to reactant consumption. Photolytic and radiolytic processes are only raised in special cases.

The subdivision of the volume into chapters is substance-oriented, which occasionally results in apparently arbitrary sections; this procedure does, however, ensure maximal clarity and fits in well with the reference nature of the work.

The first chapter *(K. H. Homann* and *A. Haas)* deals with the homogeneous decomposition of hydrides of oxygen, sulfur, nitrogen, silicon, germanium, and boron; The subject of the second *(K. F. Preston* and *R. J. Cvetanović)* is the kinetics of the decomposition of inorganic oxides (especially those of carbon, nitrogen, sulfur, fluorine, and chlorine), of sulfides and selenides (or carbon), of ozone, of certain acids of nitrogen, and of perchloric acid. The following section *(D. A. Armstrong* and *J. L. Homes)* merits particular attention; this is devoted to the decomposition of halogen compounds, especially hydrogen halides, and commendably takes account of the recent findings so important in this field. The concluding chapter *(S. J. W. Price)* deals with the decomposition of alkyl, aryl, carbonyl, and nitrosyl metal compounds. The decomposition of homonuclear diatomic molecules will be discussed in one of the subsequent volumes.

All sections are provided with extensive and instructive tables and figures, and do ample justice to the rigorous demands that may be made on the work.

O. F. Olaj [NB 225a IE]

Comprehensive Chemical Kinetics. Vol. 5. Decomposition and Isomerization of Organic Compounds. By *C. H. Bamford* and *C. F. Tipper*. Elsevier Publishing Company, Amsterdam—London—New York 1972. 1st edit., xvi, 779 pp., numerous figures, bound $ 65.75.

This volume completes Section 2 of the above work. Subdivision according to chemical classes has again been adopted throughout, which allows rapid orientation and almost entirely eliminates overlap.

Many of the homogeneous gas reactions dealt with are considered as models of unimolecular processes; the associated experimental data were (and still are) of the greatest significance for the theory of these reactions. Furthermore, reactions in homogeneous solutions as well as pyrolytic, photolytic, photosensitized, and radiolytic processes are extensively discussed, even where the reaction course is determined by secondary reactions.

The first chapter *(K. J. Laidler* and *L. F. Loucks)* is devoted to the decomposition and isomerization reactions of hydrocarbons, the second *(E. S. Swinbourne)* to the thermal and radiation- and particle-induced decomposition of halogen compounds. The following sections deal with the thermal and photochemical decomposition of aldehydes and ketones *(T. Bérces)*, as well as the decomposition and isomerization reactions of other oxygen-containing compounds such as esters, anhydrides, ethers, alcohols, carboxylic acids, and especially peroxides *(W. H. Richardson* and *H. E. O'Neal)*. The next chapter is concerned with the unimolecular reactions of nitrogen compounds *(O. P. Strausz, H. E. Gunning,* and *J. W. Lown)*; apart from diazo compounds and azides, most attention is understandably paid to azo compounds. These last two chapters thus also contain all the important information on the two major groups of radical formers, namely peroxides and aliphatic azo compounds. The volume concludes with a chapter on the unimolecular reactions of sulfur compounds *(O. P. Strausz, H. E. Gunning,* and *J. W. Lown)*.

The positive aspects of the book again include the uniformly liberal provision of clear tables and figures and an abundance of numerical data; the delayed publication in one case deserves criticism, however. All in all, each chapter indicates that the volume is a worthy member of the series.

O. F. Olaj [NB 225b]

Analysis of Triglycerides. By *C. Litchfield*. Academic Press, New York—London 1972. xvii, 395 pp., numerous figures and tables, bound, $ 19.50.

Until 1955 the only methods available for the analysis of triglycerides were essentially fractional crystallization (*Chevreul*, 1815) and oxidative degradation (*Hilditch*, 1927—1950). Bearing in mind the number of triglyceride isomers which occur in natural fats (approximately 40—1000 in vegetable fats), these methods were quite inadequate; it was only in simple cases that the triglyceride composition could be elucidated. After 1955 a burst of activity resulted in the development of new chemical and physical methods; this subsequently drew to a close in certain areas, but some methods, *e.g.* the application of mass spectrometry to the analysis of triglycerides, are still in their infancy. It is therefore highly welcome that *Litchfield*, who has personally contributed much to the development of analytical techniques in this field, has produced a review in which the current state of knowledge is summarized in concise but unusually informative manner.

Following a brief introduction to the stereochemistry and nomenclature of triglycerides and a short historical review, the extraction of lipids and isolation of triglycerides are first described; in this context the identification of fatty acids by gas chromatography is also touched upon. The following chapters deal with methods of preparation of glyceride derivatives and with the chemical and physical processes currently available for the separation and structure elucidation of triglycerides (chromatography on Ag^+-containing carrier material;

liquid-liquid distribution; gas chromatography; fractional crystallization; chromatographic separation using Kieselgel, Florisil, Al_2O_3, and ion exchangers; partial deacylation with specific and stereospecific lipases; mass spectrometry; DTA, NMR, and IR methods). This is followed by a discussion of the chemical structure and distribution models of natural triglycerides, including the biosynthesis of fats. The last chapter contains indications on the optimal combination of known analytical methods.

In conformity with the reference nature of the work (978 literature references), the individual chapters are kept short; thanks to a very clear and critical presentation which restricts itself to essentials, they nevertheless provide not only an excellent insight into the possibilities and limitations of the different methods, but also many practical hints and suggestions.

113 figures and 62 tables, as well as meticulously produced subject, name, and literature indexes, contribute significantly to the value of the book, which belongs on the shelf of every chemist active in the lipid field.

Albrecht Fincke [NB 227 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal.

Chemical Manipulation. By *M. Faraday*. The Royal Institution Library of Science. Applied Science Publishers, Barking 1974. viii, 656 pp., bound, £ 12.00.

Gradient Liquid Chromatography. By *C. Liteanu* and *S. Gocan*. From the series "Ellis Horwood Series in Analytical Chemistry". Halsted Press New York 1974. xii, 338 pp., bound, £ 10.50.

Synthetic Reagents, Vol. II. By *J. S. Pizey*. Ellis Horwood, Chichester/Halsted Press, New York 1974. 353 pp., bound, £ 12.50.

Polymer Characterization by Thermal Methods of Analysis. Edited by *J. Chiu*. Marcel Dekker, New York 1974. xviii, 254 pp., bound, £ 14.00.

Lehrbuch der Angewandten Chemie, Vol. I: Qualitativ-anorganisches Praktikum. By *G.-O. Müller*. S Hirzel Verlag, Leipzig 1974. 391 pp., bound, 18.50 M.

Orbitale organischer Moleküle. By *W. L. Jørgensen* and *L. Salem*. Verlag Chemie, Weinheim 1974. viii, 294 pp., stitched, DM 32.— (Chemie-Paperback).

Einführung in die Röntgenfeinstrukturanalyse. By *H. Krischner*. From the series "uni-text". Vieweg, Braunschweig 1974. vi, 171 pp., stitched, DM 24.80.

Photochemistry, Vol. 5. Senior Reporter: *D. Bryce-Smith*. The Chemical Society, London 1974. xi, 789 pp., bound, £ 20.00.—A volume of the series "Specialist Periodical Reports".

Solid State Reactions. By *H. Schmalzried*. From the series "Materials Science Series". Verlag Chemie, Weinheim/Academic Press, New York 1974. x, 214 pp., bound, DM 54.—.

The Solid State of Polymers. Edited by *P. H. Geil, E. Baer*, and *Y. Wada*. Marcel Dekker, New York 1974. xi, 708 pp., bound, £ 16.25.

Introduction to Organic Electrochemistry. By *M. R. Rifi* and *F. H. Cowitz*. From the series "Techniques and Applications in Organic Synthesis". Marcel Dekker, New York 1974. vii, 417 pp., bound, $ 26.50.

The Structural Chemistry of Phosphorus. By *D. E. C. Corbridge*. Elsevier Scientific Publishing Company, Amsterdam 1974. xiii, 542 pp., bound, Dfl. 75.00.

Pericyclic Reactions. By *G. B. Gill* and *M. R. Willis*. From the series "Chapman and Hall Chemistry Textbook Series". Edited by *R. P. Bell, N. N. Greenwood*, and *R. O. C. Norman*. Chapman and Hall, London 1974. viii, 240 pp., stitched, £ 2.95.

Organic Photochemistry. By *J. M. Coxon* and *B. Halton*. From the series "Cambridge Chemistry Texts". Edited by *E. A. V. Ebsworth, D. T. Elmore, P. J. Padley*, and *K. Schofield*. Cambridge University Press, London 1974. vii, 196 pp., stitched, £ 1.90.

Applications of Liquid Scientillation Counting. By *D. L. Horrocks*. Academic Press, New York 1974. xiii, 346 pp., bound, $ 29.50.

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Modern Methods for the Study of Electrode Processes

By Joachim Heitbaum and Wolf Vielstich[*]

The investigation of electrode processes calls for the use of methods that yield information on the reaction mechanism and the reaction rate, on the nature and stability of intermediates, and on adsorption processes at the electrode. It is no longer enough to record current-voltage curves or charging curves. In addition to the potentiostatic scan method, other methods that have proved useful for the investigation of electrode kinetics are the rotating disc electrode in particular, and to a smaller extent AC polarography. Intermediates can be identified with rotating double electrodes and by ESR spectroscopy or mass spectrometry. Adsorption processes on electrode surfaces can be studied by optical methods or by radioactive tracer methods.

1. Introduction

In the study of electrode processes, there are three phenomena in particular that are of interest to the scientist. These are the electrode kinetics (mechanism and rate of an electrochemical process), the occurrence of intermediates (free radicals, radical-ions), and adsorption (of the starting substance and of intermediates) on the electrode surface.

For experimental investigations, various methods are available, depending on the nature of the effect to be studied. Apart from potentiostatic and galvanostatic pulse methods, other methods that have proved useful for the study of electrode kinetics are primarily the potential scan method, the rotating disc method, and modern polarographic methods (AC polarography); intermediates of an electrochemical reaction can be detected and identified with the rotating double electrode (ring-disc or ring-ring) and by optical methods (reflection spectroscopy, electroluminescence). Free-radical intermediates, particularly in organic reactions, can be studied by ESR spectroscopy. Adsorption on the electrode surface or in the electrolytic double layer can be investigated by optical methods (absorption and reflection spectroscopy) and by tracer methods (use of radioactively labeled substances), as well as by the conventional AC measurement.

These methods and their possible combinations will be discussed below. Experimental details and results will be described only in so far as this seems necessary for an understanding of the measuring principle and of the scope of the methods.

2. The Potentiostatic Scan Method

2.1. Measuring Principle

The essential feature of the potentiostatic scan method is a linear variation of the potential of the working electrode between two reversal points (Fig. 1). For most investigations the reversal points chosen should preferably be the potentials

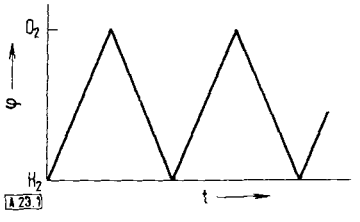
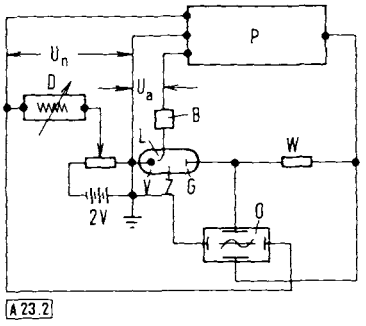


Fig. 1. Variation of potential with time on the measuring electrode in the potentiostatic scan method; potential scanning rate between a few mV/s and 1 V/s. φ = potential, t = time.

of anodic oxygen and cathodic hydrogen evolution, respectively. Electrode poisons are thus constantly removed by oxidation or reduction and the electrode is reproducibly activated.

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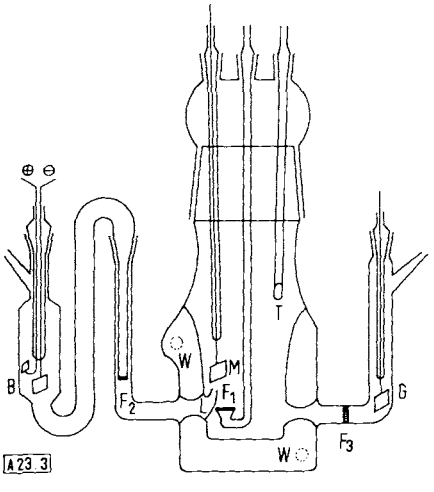
Figure 2 shows the block circuit diagram for the application of the potentiostatic scan method. To achieve a strictly linear variation of the potential of the test electrode, the potential difference between the working electrode and a reference elec-



A 23.2

Fig. 2. Experimental device for the potentiostatic scan method. Z = electrolysis cell, V = test electrode, G = counter electrode, B = reference electrode, D = triangular potential wave generator, P = potentiostat, O = oscillograph, W = resistance, L = Luggin capillary. $U_n = U_{nominal}$, $U_a = U_{actual}$.

trode (U_{actual}) must be constantly compared, by means of an electronic potentiostat, with the voltage produced by a triangular potential wave generator ($U_{nominal}$). With a time constant of $\tau < 10^{-5}$ s, the potentiostat equalizes the actual voltage and the nominal voltage by passing a current through the working electrode and the counterelectrode. This current is measured as a function of the electrode potential. The potential scanning rate of the triangular voltage generator can be varied between a few mV/s and 1 V/s. An experimental arrangement of this type was first used by *Knorr* and *Will*[1], for investigation of hydrogen and oxygen films on noble metals.

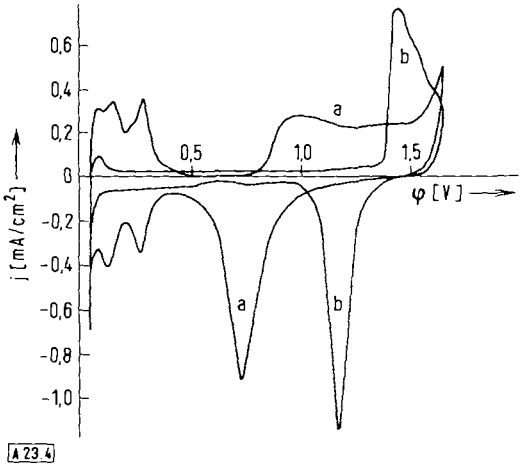


A 23.3

Fig. 3. Electrochemical cell for the application of the potential scan method. M = working electrode, G = counter electrode, B = hydrogen reference electrode, F_1, F_2, F_3 = sintered glass plates, L = Luggin capillary, T = thermometer, W = water ducts to thermostat jacket.

Figure 3 shows an example of a thermostatically controllable electrolysis cell. The working electrode M can be flushed with gas through a sintered glass plate F_1. The counterelectrode and the hydrogen reference electrode B are separated from the working-electrode electrolyte compartment by sintered glass separators F_3 and F_2 respectively. (For further details of the electrolysis cell see [2].)

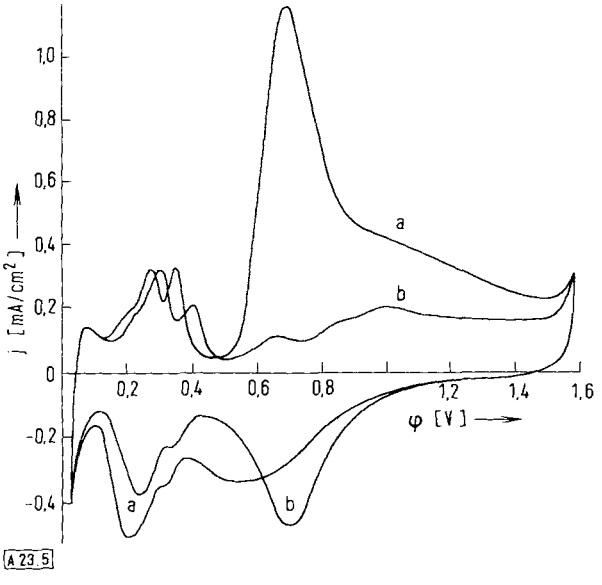
At smooth platinum in pure sulfuric acid, if the potential of the working electrode is allowed to sweep the range between the start of hydrogen evolution and the start of oxygen evolution, one obtains the current-potential diagram shown in Figure 4, curve a. Since there are no electrochemically active substances in the electrolyte, one observes the build-up and breakdown of chemisorbed hydrogen and oxygen films, the "surface-layer diagram". The nature of the surface-layer diagram depends very strongly on the electrode material used, and to a smaller extent on the electrolyte solution[3]. The surface-layer diagram for a smooth gold electrode in H_2SO_4 (Fig. 4, curve b) shows that the coverage of gold with hydrogen, unlike that of platinum, is very low, and that coverage with oxygen begins sharply only at +1250 mV. Investigations on gold can therefore be carried out over a wide range of potentials without interference from surface-layer currents. (For detailed discussions of surface-layer diagrams see [1–3].)



A 23.4

Fig. 4. Surface-layer diagrams in 1 N H_2SO_4 at room temperature, 100 mV s. N_2 flushing a) on platinum, b) on gold. φ = potential, j = current density.

If an electrochemically active substance is added to the electrolyte, the surface-layer currents and the current-potential characteristics are superimposed. This is shown in Figure 5 for the anodic oxidation of NH_3 in 1 M KOH on platinum. The surface-layer currents can often be eliminated by a suitable choice of the potential scanning rate. With slow potential



A 23.5

Fig. 5. Current-potential diagram a) on smooth platinum in 1 M KOH with 10^{-3} M NH_4OH, 20 °C, 100 mV/s. N_2 flushing; for comparison b) surface-layer diagram on smooth platinum in 1 M KOH. φ = potential, j = current density.

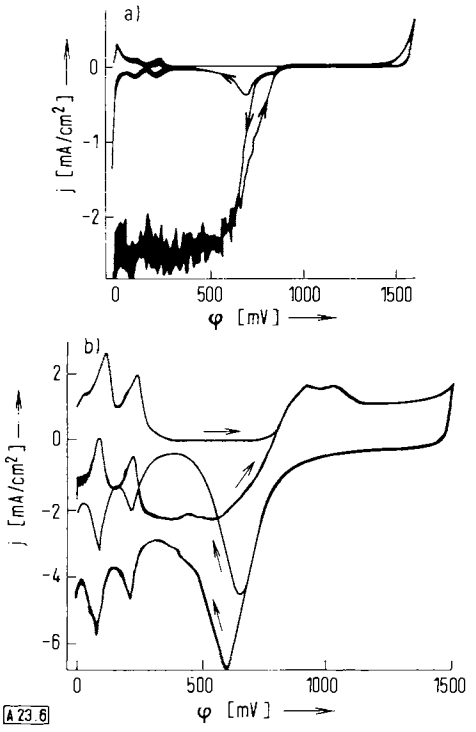


Fig. 6. Current-potential diagram on smooth platinum with O_2 flushing. a) Development of an O_2 diffusion limiting current with slow potential scanning (30 mV/s); top: electrode flushed with N_2; bottom: electrode flushed with O_2. b) Fast scanning (1 V/s); top: electrode flushed with N_2; bottom: electrode flushed with O_2. φ = potential, j = current density.

scanning and a high rate of the electrode reaction, the surface-layer current makes only a negligible contribution to the total current. This is illustrated in Figure 6a for the reduction of oxygen on smooth platinum in H_2SO_4. A cathodic diffusion limiting current develops. With fast potential scanning the surface-layer current is no longer negligible (Figure 6b). The build-up and breakdown of the hydrogen layer and the reduction of oxygen overlap. It can be seen from the diagram that the two processes proceed independently of each other[4, 5].

In many cases the addition of an electrochemically active substance to the electrolyte leads, not simply to a limiting current as in Figure 6a, but to a series of anodic or cathodic current maxima, *i.e.* to an electrochemical spectrum. As an example, Figure 7 shows the current potential diagram of ethanol in H_2SO_4 on smooth platinum. There are three anodic current maxima. Since the electrode was flushed with nitrogen during the recording of this spectrum, the current maxima are not due to a decrease of the electrochemically active substance on the electrode, but result from the inhibiting adsorption of reactants and/or intermediates or, as in the present case, from the inhibiting effect of two kinds of chemisorbed oxygen.

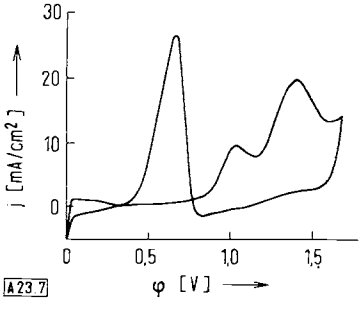


Fig. 7. Current-potential diagram of ethanol on smooth platinum in 1 N H_2SO_4, 350 mV/s, N_2 flushing. φ = potential, j = current density.

2.2. Net Diagrams

Experimental separation of the surface-layer currents from the current potential characteristic of an electrochemically active substance is impossible if the part of the current due to the electrochemical reaction of the active substance is low. As was shown in Figure 5, the interpretation of the electrochemical spectrum is very difficult in such a case, since it is very hard to distinguish between the influence of the surface layer formation and the electrochemical reaction. In cases of this type it seems reasonable to determine the point-by-point difference between the current potential curves obtained in the presence and in the absence of the electrochemically active substance.

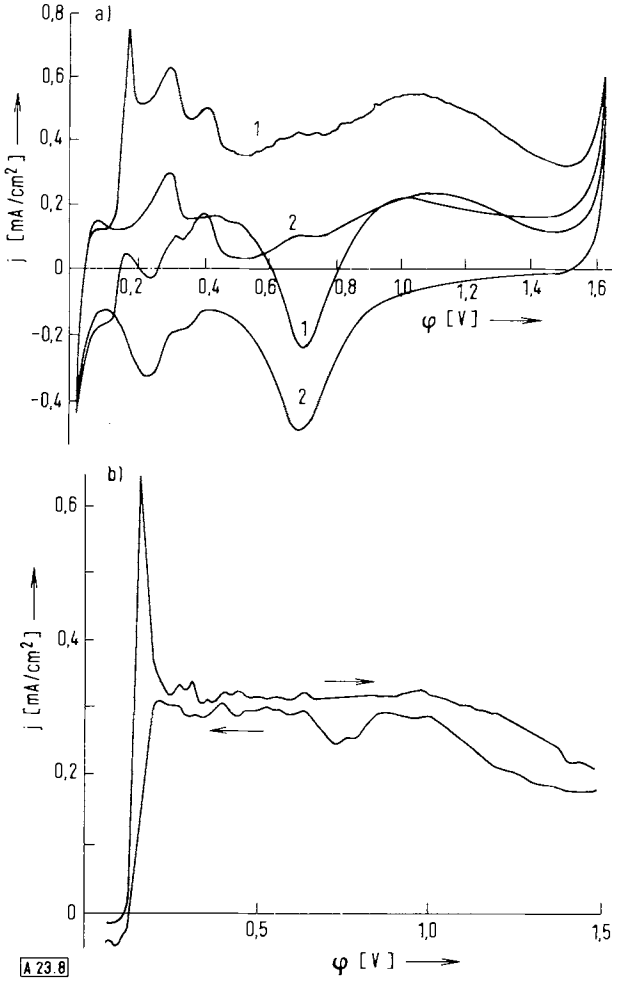


Fig. 8. a) Current-potential diagram on smooth platinum in 1 M KOH + 10^{-4} M N_2H_4, 20 °C, 100 mV/s. N_2 flushing (curve 1); for comparison the surface-layer diagram in 1 M KOH (curve 2). b) Net diagram on smooth platinum in 1 M KOH + 10^{-4} M N_2H_4; the diagram was plotted from the point-by-point differences between curve 1 and curve 2 in a). φ = potential, j = current density.

To illustrate this, Figure 8a shows the current potential curve on smooth platinum in pure KOH (curve 2) and in KOH + 10^{-4} M hydrazine (curve 1). Subtraction of one curve from the other gives the net diagram shown in Figure 8b for the anodic oxidation of hydrazine on platinum[6]. After an initial elimination of hydrogen (the sharp current peak in the anodic sweep

is due to nascent hydrogen), a diffusion limiting current is established at the electrode. A slight decrease in the current is observed at potentials above 1 V, due to the inhibitory effect of the adsorbed oxygen.

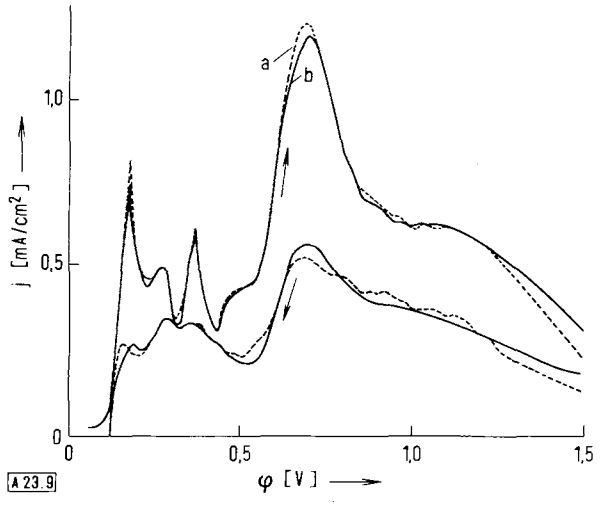


Fig. 9. Net diagram for the superposition of the oxidation of ammonia and of hydrazine on smooth platinum in 1 M KOH + 10^{-3} M NH_4OH + 10^{-4} M N_2H_4, 20 °C, 100 mV/s, N_2 flushing; a) mathematical summation of the net curves for N_2H_4 and NH_4OH; b) experimental sum curve for the simultaneous presence of both substances in the electrolyte. φ = potential, j = current density.

This technique of deriving net diagrams is very suitable for the investigation of the mutual effects of simultaneous electrode reactions. This will be illustrated for the superimposed oxidation of ammonia and of hydrazine on smooth platinum[6]. The net diagrams for hydrazine and for ammonia are first constructed separately by the procedure described above, and the calculated sum curve is obtained. This calculated sum curve corresponds to the case where the two electrochemical processes take place together without inhibition. The experimental sum curve is obtained by recording the current potential diagram for the simultaneous oxidation of NH_3 and N_2H_4. Figure 9 shows both the calculated and the experimental sum curves. The close agreement between curves a and b shows that hydrazine and ammonia are oxidized independently of each other over the entire range of potentials.

2.3. Special Applications of the Potentiostatic Scan Method

Since the surface layer diagrams on different electrode metals are very different from one another, the potentiostatic method can be used for the identification of electrode metals. In particular, the composition of the electrode surface can be determined in the case of alloys[7]. This is particularly successful when the potentials of the oxygen reduction peaks of the alloy components are as far apart as possible. Figure 10 shows the surface layer diagram of a platinum gold alloy. The oxygen chemisorbed on gold is clearly reduced more readily than that chemisorbed on platinum.

By recording current potential diagrams on rotating electrodes, it is very easy to detect whether intermediates involved in the charge transfer reaction pass into solution. On a rotating electrode the intermediates formed are transported more rapidly into the bulk of the solution by the flow on the electrode surface; a smaller current should therefore be

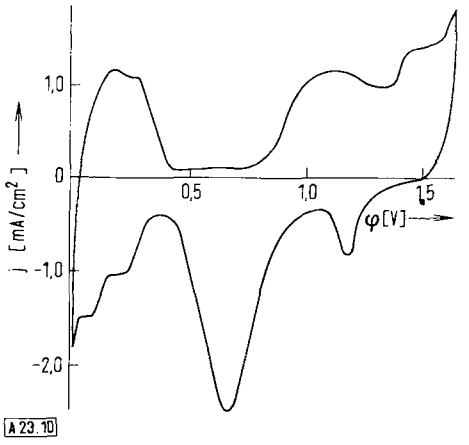


Fig. 10. Surface-layer diagram of a platinum-gold alloy (Pt:Au = 40:60) in 1 N H_2SO_4, 100 mV/s, N_2 flushing. φ = potential, j = current density.

obtained with rotation than without in such a case. This is shown in Figure 11 for the oxidation of methanol in H_2SO_4 on smooth platinum.

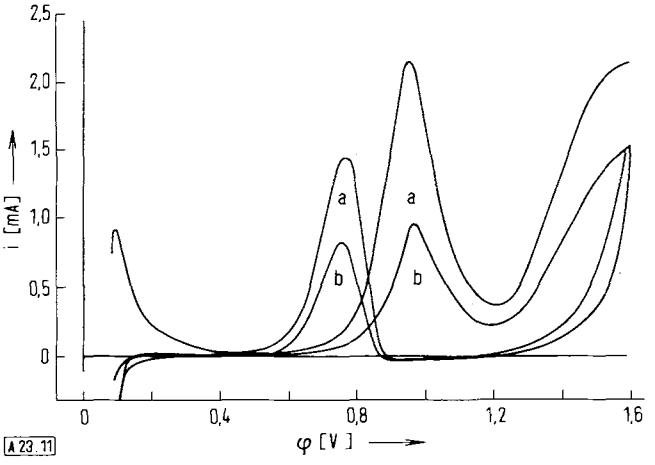


Fig. 11. Current-potential diagram on smooth platinum in 1 N H_2SO_4 + 1 M CH_3OH recorded a) on a rotating electrode (75 Hz); b) without rotation; 100 mV/s. φ = potential; i = current.

The current maxima are distinctly higher without rotation of the electrode (curve a) than on the rotating electrode (curve b). The soluble intermediates are formaldehyde and formic acid. The magnitude of the effect depends on the potential scanning rate. A fast potential variation accelerates the electrode reaction so strongly that only small quantities of the intermediates are transported away into the solution. In this case there is only a slight difference between the diagrams with and without rotation.

3. Rotating Electrodes

3.1. Measuring Principle

The problem in studies on electrode kinetics often lies in the elimination of transport phenomena. *Levich*[8] in 1942 therefore suggested the use of a rotating disc as the measuring electrode. In a practical device it consists of a metal disc sunk into the center of the front area of a plastic cylinder (Figure 12) which rotates in the electrolyte solution. As the cylinder rotates, the solution is sucked along its axis of rotation and thrown radially across the front area, as illustrated in

Figure 13. This leads to the establishment of a constant Prandtl flow boundary layer δ_{Pr} over the entire front area of the cylinder, and hence, according to the equation

$$\delta_N = \left(\frac{D}{\nu}\right)^{1/3} \delta_{Pr}$$

to a concentration profile that is independent of the radius of the electrode (δ_N = Nernst diffusion layer, D = diffusion coefficient, ν = kinematic viscosity). Since

$$j = zFD \frac{c^0}{\delta_N}$$

one obtains a uniform current density j over the disc electrode (z = charge number, F = Faraday constant, c^0 = concentration). Pure mass transport leads to the establishment of a diffusion limiting current j_{gr}, whose magnitude depends on the speed of rotation ω of the electrode. According to *Levich*[9] and *Gregory* and *Riddiford*[10], the equation

$$j_{gr} = \frac{zFD^{2/3}\nu^{-1.6}c^0}{1.6126 + \left(\frac{D}{\nu}\right)^{0.36} \times 0.5704}\omega^{1/2} \qquad (1)$$

is valid in this case.

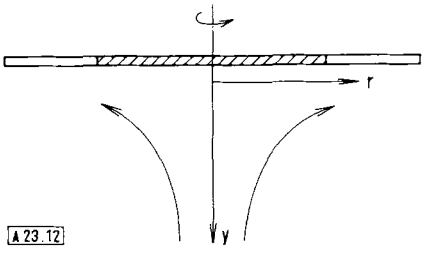


Fig. 12. Flow on the front area of a rotating cylinder with inset disc electrode (shaded); y = axis of rotation, r = radius.

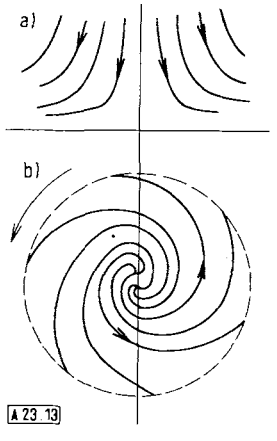


Fig. 13. Flow lines on the front area of a rotating cylinder; a) section, b) elevation.

Figure 14 shows a section through the apparatus, with the electrolysis cell[11]. The motor connected to the cylinder allows rotation speeds of between a few Hz and a few hundred Hz. The rotation speed is recorded by means of a light beam and a perforated disc, and is adjustable with an accuracy of 0.1 Hz.

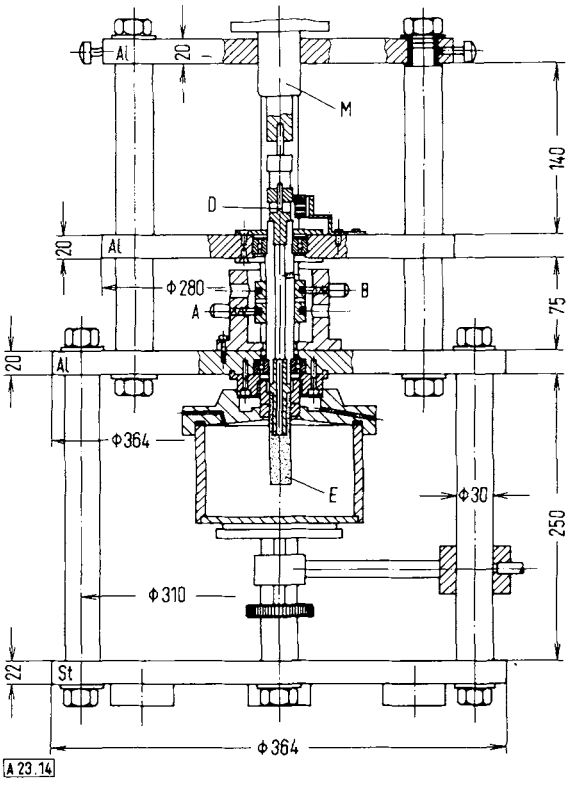


Fig. 14. Measuring apparatus with rotating electrode, in cross section. A, B = current collectors for disc and ring electrode, respectively, D = revolution counter, E = electrode, M = motor, St = steel plate, Al = aluminum discs.

3.2. Possible Applications of the Rotating Disc Electrode

3.2.1. Precision Determination of Diffusion Coefficients

If the rate of an electrochemical reaction is determined exclusively by mass transport (the discharge step is extremely fast) a diffusion current is set up at the electrode and increases, according to eq. (1), in proportion to $\sqrt{\omega}$. According to eq. (1), therefore, the diffusion coefficient D can be determined if the concentration c^0 is known, or the concentration c^0 can be determined if the diffusion coefficient is known, from a plot of j against $\sqrt{\omega}$.

Gostiša-Michelčič, *Vielstich*, and *Heindrichs*[12] have used this method for the precision determination of the trace diffusion coefficient of the proton in KCl. This involves, not the diffusion of the proton, but the rate of charge transfer in protonic solution (hopping mechanism *via* hydrogen bonds). Figure 15 shows the measured diffusion limiting currents for several rotation speeds between 31 and 183 Hz with a smooth platinum disc electrode. The slope of the straight lines in the plot of j_{gr} against $\sqrt{\omega}$ gives the apparent diffusion coefficient of the proton with an accuracy of $\pm 0.3\,\%$. The value found for 25 °C was $D_{H^+} = 74.6 \times 10^{-6} \pm 0.3\,\%$. The accuracy of the method is therefore better by a factor of 5 to 10 than that of the usual methods (polarography, diffusion after *Cottrel*).

3.2.2. Determination of the Characteristic Data of a Charge-Transfer Reaction

Before the current potential curve passes over into the limiting current determined purely by mass transport, both the convective diffusion and the charge-transfer are rate-determining for the reaction. Measurement of the current as a function of the rotation speed ω in this potential range yields informa-

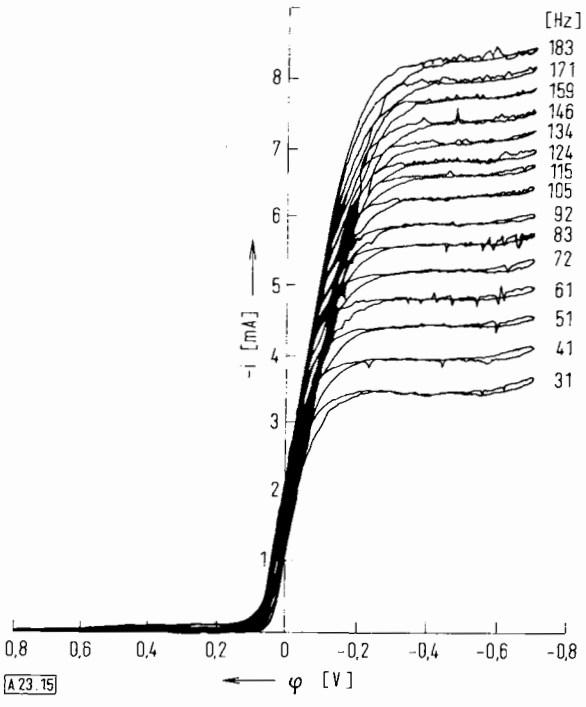


Fig. 15. Current-potential curves (diffusion limiting currents) on a rotating platinum electrode as a function of the speed of rotation in 1 M KCl + 3×10^{-3} M HCl. φ = potential, i = current.

tion about the rate of the electrode reaction if the influence of mass transport is eliminated by extrapolation to $\omega \rightarrow \infty$. *Jahn* and *Vielstich*[13] have derived the following equation for this case:

$$\frac{1}{j} = \frac{1}{j_D} + \frac{1}{j_D} K \frac{1}{\sqrt{\omega}} \tag{2}$$

where j_D is the pure charge-transfer current corresponding to a given overpotential η. j_D can be determined from the intercept on the axis in a plot of $1/j$ *against* $1/\sqrt{\omega}$ for a fixed η (Fig. 16). A series of pairs of values (j_D, η) then yields the pure charge-transfer current potential curve, from which the transfer coefficient α and the exchange current density j_0 can be deduced.

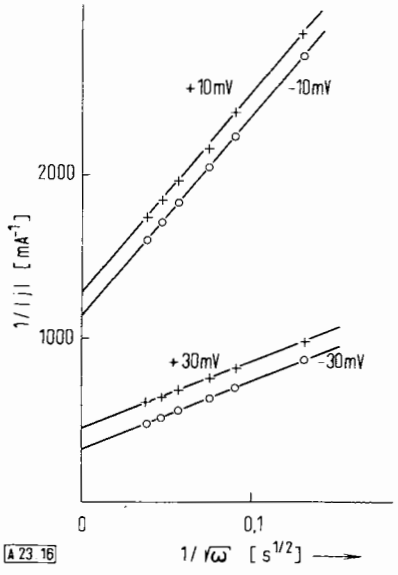


Fig. 16. Plot of $1/|j|$ against $1/\sqrt{\omega}$ for the determination of the charge transfer current density j_D (the parameter is the overpotential η) for the system 10^{-2} M $Fe^{2+}/10^{-2}$ M Fe^{3+} in 1 M $HClO_4$ on smooth platinum. ω = speed of rotation, j = current density.

Jahn and *Vielstich*[13] have tested this method on the system Fe^{2+}/Fe^{3+} in $HClO_4$. The good fit of the experimental points with the connecting straight lines in Figure 16 is a measure of the accuracy of the method. They found a value of 0.23 A/cm² for the standard exchange current density of the system indicated; the transfer coefficient was 0.63.

3.2.3. Determination of the Rate Constants of a Preceding Chemical Reaction

It was explained on the basis of eq. (1) that for pure mass transport the diffusion limiting current on the rotating electrode increases in proportion to $\sqrt{\omega}$. However, if the electrochemical reaction is preceded by an inhibited reaction step (adsorption on the electrode, chemical reaction), derivations from linearity are found at high rotation speeds, as indicated in Figure 17a.

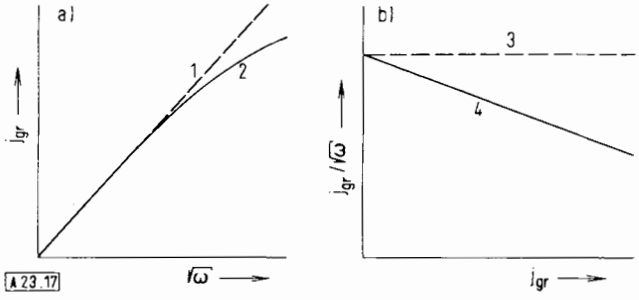


Fig. 17. a) Limiting currents on a rotating electrode plotted against $\sqrt{\omega}$; curve 1, with pure mass transport; curve 2, deviation with kinetic inhibition. b) $j_{gr}/\sqrt{\omega}$ against j_{gr}; curve 3, with pure mass transport; curve 4, with kinetic inhibition. ω = speed of rotation, j_{gr} = reaction limiting current density.

A typical example is the evolution of hydrogen from a weak acid HA, where the protons that react in the charge-transfer reaction are formed by a preceding dissociation on the electrode surface:

$$\begin{aligned} &HA \underset{k_r}{\overset{k_d}{\rightleftharpoons}} H^{\oplus} + A^{\ominus} \\ &H^{\oplus} + e^{\ominus} \rightarrow \tfrac{1}{2} H_2 \end{aligned} \tag{3}$$

The rate of the preceding reaction (*i.e.* the dissociation rate of the weak acid in the above example) can be found from the deviation of the current from the proportionality to $\sqrt{\omega}$ that would exist without reaction inhibition.

According to *Koutecki* and *Levich*[14] and to *Vielstich* and *Jahn*[13], the following relation is valid in this case:

$$\frac{j_{gr}}{\sqrt{\omega}} = \frac{j_{gr,diff}}{\sqrt{\omega}} - \frac{D^{1/6} c_{A^{\ominus}}^{1,2} j_{gr}}{1.61 \cdot \nu^{1/6} (k_d/k_r) \sqrt{k_r}} \tag{4}$$

where j_{gr} is the measured reaction limiting current density and $j_{gr,diff}$ is the limiting current density due to the mass transport. According to eq. (4), a plot of $j_{gr}/\sqrt{\omega}$ against j_{gr}, as in Figure 17b, gives a horizontal straight line for pure mass transport. In the case of reaction inhibition one obtains a straight line with a negative gradient, from which the dissociation rate constant k_d can be calculated according to eq. (4). D, ν, $c_{A^{\ominus}}$, and the equilibrium constant k_d/k_r must naturally be known from thermodynamic measurements or conductivity measurements.

Gostiša-Mihelčič and *Vielstich*[15] have used this method to determine the dissociation constants of acetic and formic acids. Figure 18 shows $j_{gr}/\sqrt{\omega}$ as a function of j_{gr} for the system

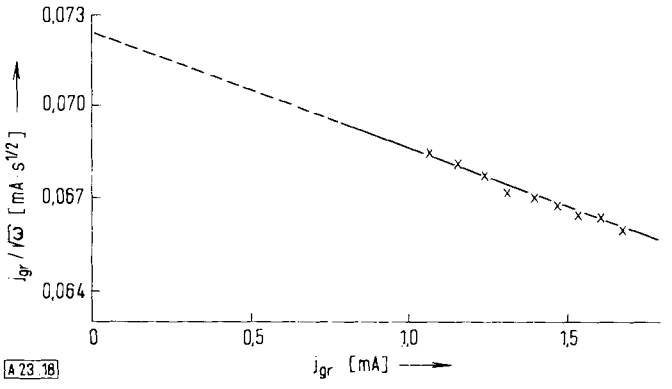


Fig. 18. $j_{gr}/\sqrt{\omega}$ *vs.* j_{gr} plotted for the system acetic acid/sodium acetate; 2.73×10^{-3} M HAc + 3×10^{-2} M NaAc + 1 M KCl, measured on a rotating platinum disc electrode. pH = 5.66. j_{gr} = reaction limiting current density. ω = speed of rotation.

acetic acid/sodium acetate from measurements on a smooth platinum disc electrode. The value found for the dissociation rate constant from the slope of the straight line is $k_d = 5.4 \times 10^5\,s^{-1}$. The diffusion coefficient of acetic acid, $D = 1.2 \times 10^5\,cm^2/s$, can also be found from the intercept of the straight line on the ordinate. A similar experiment gave a dissociation rate constant $k_d = 4.9 \times 10^6\,s^{-1}$ for formic acid. Owing to the higher rate of dissociation of formic acid, this constant was obtainable only by the use of rotation speeds of a few hundred Hz.

3.2.4. Separation of Kinetic and Transport-Controlled Reactions

If two electrochemical reactions proceed simultaneously in the potential range studied, the current components can be separated if one of the reactions is transport-controlled while the rate of the other is kinetically controlled.

According to eq. (1), to a change $\Delta\omega^{1/2}$ in the speed of rotation of a rotating electrode there corresponds a current signal Δi, which is determined exclusively by the transport-controlled component of the current. *Miller*[16] has therefore suggested the superposition of a periodic change $\Delta\omega^{1/2}$ (*e.g.* sinusoidal or rectangular) on a fixed value $\omega_0^{1/2}$, this periodic change

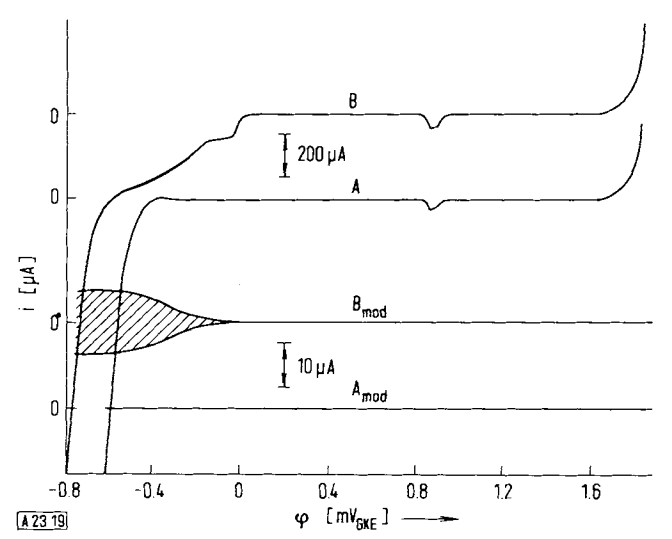


Fig. 19. Cathodic current potential diagram on gold at 26.6 Hz, potential scanning rate 5 mV/s (after [16]). a) in 1 M H_2SO_4; $a_{mod.}$) as a with superimposed sinusoidal frequency modulation; b) in 1 M H_2SO_4 + 2 M $CuSO_4$; $b_{mod.}$) as b with superimposed frequency modulation. φ = potential, i = current.

being so slow that the condition for eq. (1), *i.e.* the establishment of a steady state hydrodynamic flow, is not violated. In this case

$$\frac{\Delta i}{\Delta\omega^{1/2}} = \frac{i_{transp.}}{\omega_0^{1/2}}$$

For given $\omega_0^{1/2}$ and $\Delta\omega^{1/2}$ and measured Δi, it is possible to calculate the pure transport component $i_{transp.}$ and to compare it with the current i found without modulation.

As an example, Figure 19 shows the superposition of a copper deposition controlled by convective diffusion and the evolution of hydrogen, the kinetics of which are rate-determining at gold electrodes in particular. The splitting of the current signal by Δi in the case of the copper deposition can be seen in curve $b_{mod.}$. No Δi corresponding to the frequency modulation is observed in the evolution of hydrogen only (curve $a_{mod.}$).

3.3. The Rotating Double Electrode and Its Applications

The possibilities of a rotating system can be considerably extended if instead of a single electrode one uses several concentric electrodes (disc-ring, ring-ring). A substance formed on the inner electrode is then transported by the radial flow to the outer electrode, where it may undergo a further electrochemical reaction. The narrower the electrodes and the thinner the insulating layer between them, the greater is the sensitivity. Thus with a double ring electrode having a diameter of 10 mm, an electrode width of 1 mm, and an interelectrode distance of 0.1 mm, intermediates having a lifetime of 10^{-5} s can be detected at 400 Hz.

With the aid of this method, *Hamann* and *Vielstich*[17] were able to show that formate is formed as an intermediate in the alkaline electrolyte during the anodic oxidation of carbon monoxide to carbonate. It was not possible to show this directly with a double electrode, since CO and formate react in the same potential range on most electrodes and the oxidation of formate is blocked by carbon monoxide. The detection of formate as an intermediate in the oxidation of CO was made possible only by the use of an outer electrode ring of palladium, an electrocatalyst that is substantially selective for formate.

It can be seen from the foregoing that the double electrode is particularly suitable for the study of short-lived intermediates. However, a measuring arrangement of this type also allows the detection of homogeneous chemical reactions placed between two electrochemical steps. For example, if Fe^{3+} is reduced to Fe^{2+} on the inner electrode the Fe^{2+} can be reoxidized on the outer electrode if the potential chosen is correspondingly positive. The ratio of the reduction current to the oxidation current is known as the collection efficiency N. It gives the percentage of the substance formed on the inner electrode that reaches the outer electrode. N depends only on the electrode geometry selected[18].

If an oxidizing agent, *e.g.* H_2O_2, is added to the electrolyte, part of the Fe^{2+} formed on the inner electrode is oxidized by the H_2O_2 in a homogeneous chemical reaction and is lost with regard to detection on the outer electrode, and the collection efficiency accordingly decreases. The longer the time spent by the Fe^{2+} between the two electrodes, the greater is the decrease. One thus obtains a collection efficiency that

depends on the rotation speed. The rate constant of the homogeneous chemical reaction can be calculated from the variation of N with ω at a given H_2O_2 concentration[19].

4. AC Polarography

In conventional AC polarography, which was developed 30 years ago, the impedance of an electrochemical cell is measured under polarographic conditions, a low-amplitude (< 10 mV) sinusoidal alternating current being superimposed on the direct current, which increases linearly with time (saw-tooth). As a function of the linearly increasing electrode potential one obtains an AC signal that corresponds, to a first approximation, to the first derivative of the normal polarographic wave (Fig. 20), *i.e.* the potential of the current maximum agrees with the half-wave potential of the DC polarogram. This is not, in fact, a simple derivative of the DC curve, as is shown, *e.g.*, by the fact that the irregularities of the polarogram (drop peaks, maxima) are not differentiated at the same time.

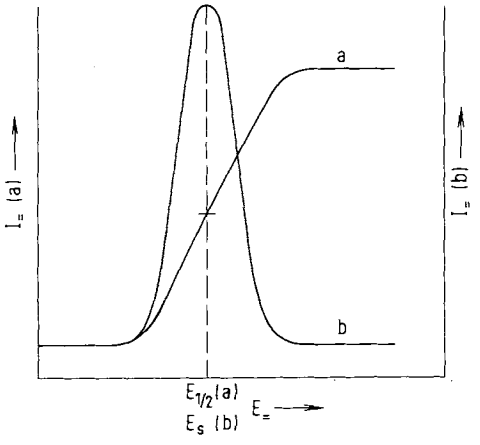


Fig. 20. Schematic representation a) of a polarographic DC step and b) the corresponding AC peak. $E_=$ = DC potential, $I_=$ and $I_\sim$ = DC and AC currents respectively; $E_{1/2}$ = half-wave potential, E_s = potential at current maximum.

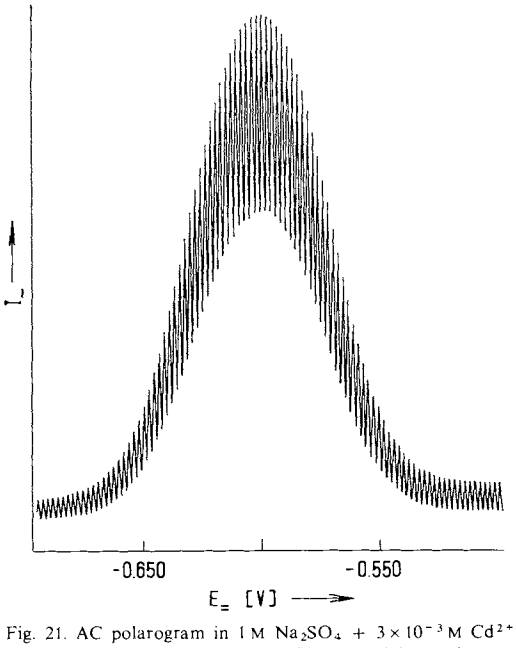


Fig. 21. AC polarogram in 1 M Na_2SO_4 + 3×10^{-3} M Cd^{2+} (after [24]), AC amplitude 5 mV, frequency 320 Hz. Potential scanning rate 25 mV/min. $E_=$ = DC potential, $I_\sim$ = alternating current.

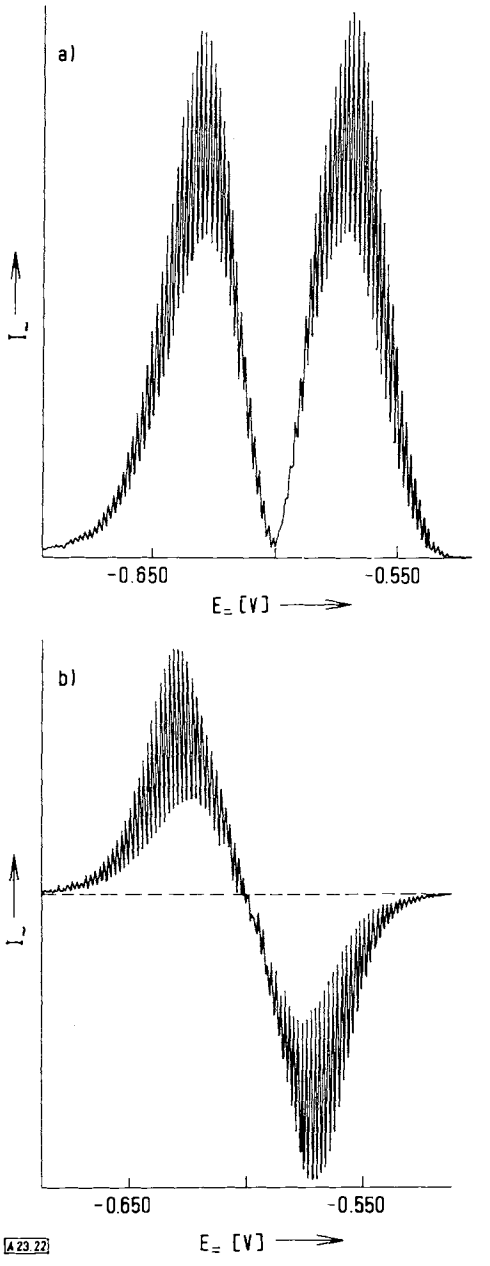


Fig. 22. Second harmonic of an AC polarogram in 1 M Na_2SO_4 + 3×10^{-3} M Cd^{2+} (after [24]), amplitude 5 mV, frequency 80 Hz, potential scanning rate 25 mV/min; a) "conventional" harmonic of an AC polarogram, b) harmonic with phase-selective recording. $E_=$ = DC potential, $I_\sim$ = alternating current.

Theoretical considerations by *Bauer et al.*[20] and by *Breyer* and *Bauer*[21] have shown that the observed AC amplitude and the corresponding real and imaginary impedance components depend on the rate constants and transfer coefficients of the reaction steps. An analysis of the AC polarogram should therefore yield information about the kinetics of the electrode reaction.

The accuracy of the measuring method is limited by the ohmic resistance of the cell and by the capacitive resistance of the double layer. The ohmic voltage drop can be largely eliminated by the introduction of a reference electrode (cf. the potential scan method), which is not usual in conventional polarography. The capacitive impedance component, on the other hand, can be reduced only by the use of a low AC frequency. In any case, the capacitive impedance is greater in AC polarography than in DC polarography, and the sensitivity is accordingly poorer in the AC method. Conventional AC polarography

has therefore never really gained acceptance for kinetic investigations.

Since the early 1960's, a new AC polarographic method has been developed, in which instead of the fundamental curve (Fig. 21), the second (or a higher) harmonic is measured with the aid of a frequency filter[22]. The capacitive current of the charge reversal of the double layer is largely free from harmonics, and the capacitive impedance is significantly lower in this type of measurement than in conventional AC polarography.

The second harmonic of an AC polarogram generally has two current maxima (Fig. 22a), which, with phase-selective measurement, have quantitatively the appearance of the second derivative of the DC polarogram (Fig. 22b). The principle of the phase-selective detector is based on a vectorial comparison of the measured voltage with a control voltage of the same frequency. The detector may be, *e. g.*, a phase-dependent rectifier[23] that passes only the component of the measured voltage that is in phase with the control voltage. The real and imaginary components of an alternating current can thus be measured directly with such an arrangement, and can then be used to find the impedance components. The phase-selective measurement therefore yields additional information about the nature of the measured (ohmic or frequency-dependent) resistance components, so that a double-layer capacity component that is still present in the second harmonic can also be eliminated.

$$X \underset{k_2}{\overset{k_1}{\rightleftharpoons}} Ox + ne^{\ominus} \rightleftharpoons R$$

(— —): $K = k_1/k_2 = \infty$, (- - -): $K = 1$, $k_1 = 1 \times 10^3\,s^{-1}$, (— · —): $K = 0.1$, $k_1 = 1 \times 10^3\,s^{-1}$. $E_= - E_{1/2}$ = difference between DC potential and half-wave potential, $I(2\omega t)$ = alternating current.

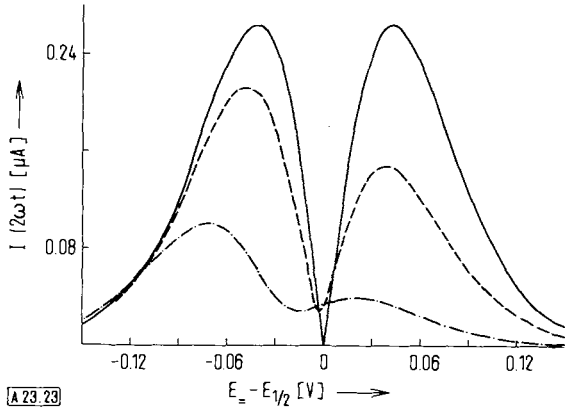


Fig. 23. Calculated second harmonic of an AC polarogram (after [24]) for the system

The shape of the first harmonic of an AC polarogram is very strongly dependent on the kinetics of the charge transfer and of the chemical reaction steps. Figure 23 shows this for the case in which a preceding chemical reaction influences the shape of the second harmonic[24].

5. Optical Methods

5.1. Absorption Spectroscopy

Optical methods are among the most promising *in-situ* techniques (measurement on the electrode surface during the electrochemical reaction) for the study of the electrochemical double layer and of the formation and consumption of reactants, intermediates, and products on or in the vicinity of the electrode surface. In absorption spectroscopy, visible or UV light is allowed to pass through a transparent electrode into the electrolyte compartment, and the quantity of light absorbed is determined. The light absorption is proportional to the concentration of the absorbing substance in the electrolyte. By varying the thickness of the layer of electrolyte, therefore, one can determine the change in the concentration of the absorbing substance as a function of distance from the electrode. Homogeneous chemical reactions that precede or follow the electrode reaction and that proceed at some distance from the electrode are thus also accessible to direct observation.

Conclusions regarding the electrode kinetics can be drawn from the change in the absorption with time during an electrode reaction. In the simple case of an electrochemical reaction $R \rightarrow Ox + ne^{\ominus}$, resulting in the formation of the light-absorbing species Ox which was not initially present in the electrolyte, the absorption M can be calculated for the case of a diffusion-inhibited reaction[25]:

$$M = \mu_0 \int_{x=0}^{x=\infty} [c_{Ox}(x)]\,dx = 2\mu_0 c_R^0 \left(\frac{D_R t}{\pi}\right)^{1/2} \qquad (5)$$

In this equation, μ_0 is the molar absorption of the substance Ox, x is the distance from the electrode, c_R^0 is the initial concentration of the substance R, and D_R is the diffusion constant of R. Eq. (5) states that in a diffusion-controlled electrode reaction, the absorption increases in proportion to $\sqrt{t}$. However, if chemical reactions are coupled with the discharge step, one finds deviations from the $\sqrt{t}$-dependence of eq. (5). The rate constant of the chemical reaction can be determined from this deviation.

Strojek and *Kuwana*[25] used this method in their studies on the oxidation of *o*-toluidine in aqueous solutions. They were able to show that the oxidation proceeds in accordance with the scheme

$$\begin{aligned} R &\longrightarrow S + e^{\ominus} \\ S &\longrightarrow Ox + e^{\ominus} \\ R + Ox &\underset{k_2}{\overset{k_1}{\rightleftharpoons}} 2S \end{aligned}$$

via an intermediate S and a subsequent synproportionation. With the aid of absorption spectroscopy, *Strojek* and *Kuwana* were able to determine the rate constants of this subsequent chemical reaction with an accuracy of about 10%.

5.2. Reflection Spectroscopy

Two fundamentally different methods are known in reflection spectroscopy. In one case the light beam is allowed to reflect several times (to increase the sensitivity) in the interior of a plane-parallel ground transparent electrode, as illustrated in Figure 24. If the angle of incidence of the light is greater than the critical angle, the light is totally reflected, provided

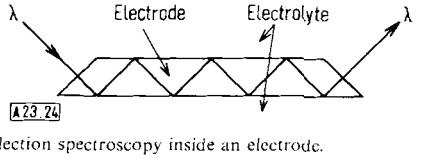


Fig. 24. Beam path in reflection spectroscopy inside an electrode.

that no substances that influence the beam path are adsorbed on the electrode surface. Theoretical considerations and practical experiments have shown that even with total reflection, the reflected beam penetrates for a distance of a fraction of a wavelength into the solution. The reflection coefficient consequently depends on the nature of the substances absorbed on the electrode.

The method has already been repeatedly used, both with visible[26, 27] and with IR light[28]. IR light appears to be particularly suitable for investigations on the surface state of semiconductor electrodes. The conditions for the use of the method in electrochemical studies are, on the one hand, that apart from the substance under investigation there are no other species (solvent, supporting electrolyte) in the solution that influence the beam path and, on the other hand, that the absorption by the adsorbed molecules is sufficiently strong. The latter condition restricts the method to investigations on fairly large organic molecules; for smaller molecules the sensitivity is insufficient for quantitative measurements[29].

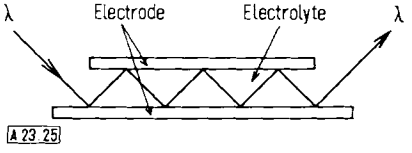


Fig. 25. Beam path in reflection spectroscopy between two electrodes.

The second method of reflection spectroscopy is used more often. In this case the light beam is allowed to reflect several times between two or more plane-parallel electrodes in the interior of the solution, as indicated in Figure 25. *Plieth*[30] recently described the theory and the possibilities of this method.

Takamura et al.[31] used a reflection cell of this type to study the oxide formation and the adsorption of foreign metal ions on gold electrodes. They used visible light and an electrode arrangement that allowed 10—15 reflections. From the dependence of the reflection on the wavelength and on the electrode potential, they were able to conclude that the change in the reflectivity depends on effects of the electric field in the double layer, on the concentration and the photoactivity of the adsorbed substances, and on the structure of the metal surface.

The method thus seems very suitable for *in-situ* studies on substances adsorbed on electrodes with visible and UV light (IR light is strongly absorbed by water and other polar solvents, and is therefore ruled out). If the wavelength dependence of the adsorbed substance can be measured, information about the nature of the specific adsorption is often obtainable (*e.g.* d-orbital interactions).

5.3. Ellipsometry

For ellipsometry one uses only a single electrode, which is irradiated with polarized light. From the change in the phase and amplitude of the polarized light it is possible not only to obtain general information about the adsorption on the electrode surface but also, in particular, to determine the thickness of a surface layer.

Figure 26 shows the principal device for ellipsometry. If one starts, for example, with a plane, homogeneous metal surface and electrochemically produces an oxide film on this electrode by means of a suitable potential, the resulting change in the refractive index of the surface layer very strongly influences the polarization of the incident light wave. This polarization change can be detected by adjusting the analyzer system ($\lambda/4$ plate and analyzer) to complete extinction (or minimum light transmission) for the pure metal electrode and measuring the quantity of light transmitted for the oxide-coated electrode with the aid of a photomultiplier. (For further details see, *e.g.*, [32].)

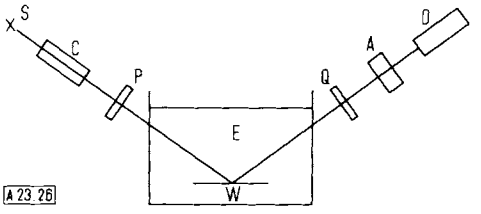


Fig. 26. Principal device of an apparatus for ellipsometry. S = light source, C = collimator, P = polarizer, Q = $\lambda/4$ plate, A = analyzer, D = detector, W = electrode, E = electrolyte.

The ellipsometric method has been used, *e.g.*, for studies of oxide formation on platinum[33] and of the passivation of nickel[34] and iron[35]. In the case of oxide formation on platinum, the coating of the electrode with oxygen, with a mean thickness of 0.2 Å, begins at 0.98 V against the normal hydrogen electrode. The thickness of the oxide layer increases linearly with the potential, and reaches a value of 6 Å at about 1.6 V, the potential at which the evolution of oxygen begins. The mean layer thickness of 0.2 Å is interpreted as being due to a partly formed monolayer.

Ellipsometric studies on the double layer have so far been carried out in most cases at only one wavelength, and consequently yield only rather unspecific information about the nature of the adsorbate layer. Measurements over a wide range of wavelengths should provide information about the interactions (nature of the bonding) that occur in the formation of monolayers on electrode surfaces.

All the optical methods described so far can be used to detect the existence of an adsorbate and to measure its film thickness and the kinetics of the adsorption, but do not allow the identification of an unknown adsorbate.

5.4. Photoelectrochemistry and Electroluminescence

Photoelectrochemistry is based on the Becquerel effect, which was discovered in 1839. *Becquerel* found that a current flows between two unequally illuminated platinum electrodes in an acidic electrolyte. The different levels of illumination of the electrodes evidently lead to the development of a potential difference, which causes the current to flow. It therefore seems reasonable to assign a "photopotential" to an electrode, this being defined simply as the potential of the illuminated electrode with respect to the potential of the unilluminated electrode:

$$\varphi^* = \varphi_L - \varphi_D$$

φ^* is the photopotential, φ_L is the potential of the illuminated electrode, and φ_D is the potential of the unilluminated electrode. The change in the potential of the electrode may be due to a series of primary and secondary effects.

Primary effects: 1, Production of excited molecules by light absorption; 2, photodissociation as a result of light absorption;

3, absorption of light by the metal, non-metal, or semiconductor, with consequent photoionization, photoemission, or change in the population of valence and conduction bands.

Secondary effects: 1, Fluorescence or phosphorescence; 2, photochemical reactions; 3, energy-transfer reactions; 4, other non-radiative de-excitation modes (inelastic collisions); 5, thermal effects (rise in temperature of the illuminated electrode).

This list shows that photoelectrochemistry allows the investigation of numerous effects by measurement of the photopotential or the photocurrent as a function of the exposure to light. The method seems promising in particular for the study of excited molecules and free radicals in organic electrode reactions and for investigations on the oxide film on solid electrodes (for discussion see [36]).

If a molecule or free radical in an excited state is formed in an electrochemical process, it may pass to the ground state with emission of light. This effect, which is known as electroluminescence, is shown in particular by aromatic hydrocarbons[36]. In certain circumstances it allows the identification of an intermediate, and is thus an important addition to the range of methods for the investigation of reaction mechanisms.

6. ESR Spectroscopy

The measuring principle of electron spin resonance spectroscopy is based on the fact that free radicals do not have saturated electron spins and are therefore paramagnetic. In a homogeneous magnetic field, the electron spin has two possible states (parallel or antiparallel to the magnetic field), whose energies are slightly different. The number of radicals in the lower energy state is slightly greater than the number in the higher state (Boltzmann distribution). If energy is supplied to the system in the form of electromagnetic radiation (microwaves) whose energy is exactly equal to the energy difference between the two states, radicals pass from the lower energy level to the higher. This is opposed, however, by the fact that radicals from the higher energy level relax to the lower level as a result of interaction with the environment (spin-lattice interaction). In the resonance case (injected energy = energy difference between the states) this leads to a continuous measurable absorption of the microwave radiation.

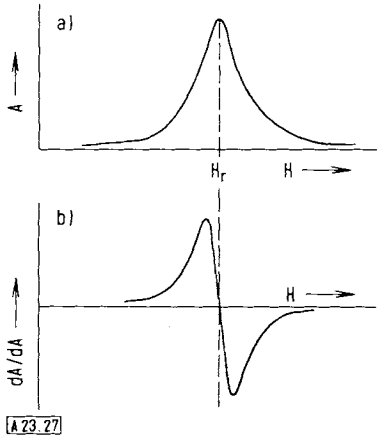


Fig. 27. a) Absorption A as a function of the field strength H. b) First derivative of the absorption curve dA/dH (H_r = resonance field strength).

In the measurements, the strength of the homogeneous magnetic field is varied linearly and the energy absorbed is measured. This gives an absorption curve as shown in Figure 27a, with a maximum at the point of resonance. However, the first derivative is recorded in most cases (Fig. 27b). Interaction of the electron spins with the magnetic moments of the atomic nuclei of the molecules (protons and nitrogen in the case of organic substances; ^{12}C and ^{16}O have no magnetic moment) leads to a splitting of the resonance line (hyperfine structure). The number of hyperfine structure lines can be considerable in the case of organic molecules. As an example, Figure 28 shows the ESR spectrum of the nitrobenzene radical-anion, with 54 hyperfine structure lines.

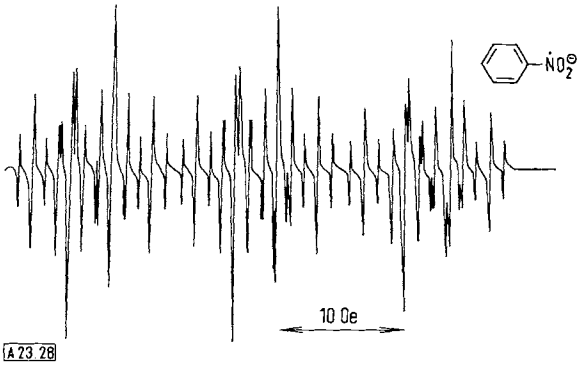


Fig. 28. ESR spectrum of the nitrobenzene radical-anion in aqueous alkali solution (after [37]). The 54 lines observed correspond to the splitting due to the ^{14}N nucleus, one proton (*para*), and two groups of two equivalent protons each (*ortho* and *meta*).

Analysis of the hyperfine structure splitting of the ESR spectrum with regard to the number, intensity, and spacing of the lines yields information on the number and nature (H or N) of atomic nuclei that influence the electron spin. In many cases the molecular structure of the radical can be deduced, *i.e.* the radical can be identified.

The microwaves are injected by means of a cavity resonator inside which the radicals either flow through a thin capillary (external production of free radicals, Fig. 29a), or are directly produced in a shallow cell (internal production of free radicals, Fig. 29b). In the former case, not only is it possible to identify

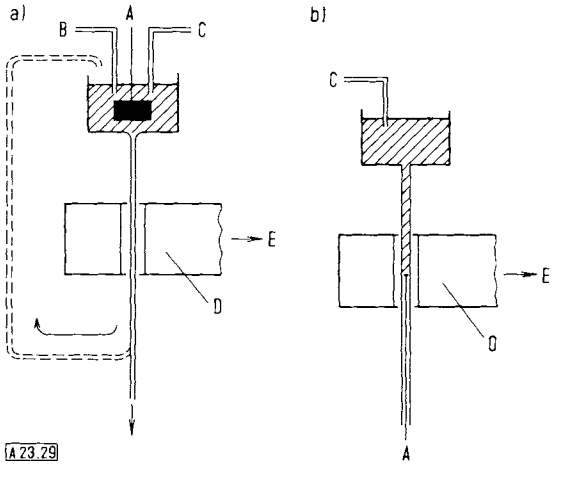


Fig. 29. Scheme of an apparatus for ESR measurements (after [37]) with a) external generation of free radicals, b) internal generation of free radicals. A = working electrode, B, C = connections to reference electrode and counter-electrode, D = microwave resonator, E = hollow conductor connection; magnetic field normal to the plane of the drawing.

the radical-ion, but its lifetime can also be determined by variation of the distance from the point at which it is formed to the measuring position. Moreover, if the flow capillary is branched, a reagent solution may be added, and free-radical reactions can thus also be studied (Fig. 30). The method with internal production of the free radicals can be used for the study of short-lived intermediates.

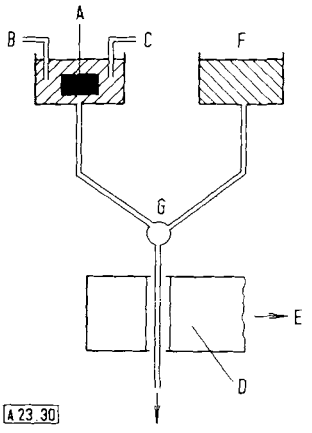


Fig. 30. Scheme of an apparatus with external production of free radicals and mixing with a reagent solution before the ESR measurement (after [37]). A to E as in Fig. 29. F = storage vessel for reagent solution, G = mixing chamber.

As far as electrochemical investigations are concerned, the most important results of ESR measurements are the proof of the presence of free radicals and the determination of their molecular structure. It is also possible to determine absolute or relative concentrations; this is important for kinetics. Further information can be obtained from the hyperfine structure splitting (energies of molecular orbitals) and from the line width (solvation processes, ion-pair formation). ESR spectroscopy thus provides numerous data for electrochemical investigations (for examples see [37]).

7. Radioactive Tracer Methods

In addition to the foregoing methods for the investigation of the electrolytic double layer and the specific adsorption of ions, intermediates, *etc.* on the electrode surface, radioactively labeled substances have frequently also been used for this purpose in recent years. However, the radioactive tracer method did not attain any importance until radioactive isotopes of practically all elements became available *e.g.* as products from nuclear reactors.

The following is an example of a procedure that can be used for the study of the adsorption of organic molecules on metal electrodes. The electrode is immersed in an electrolyte containing the radioactively labeled form of the molecules to be investigated. The adsorption begins immediately after the immersion of the electrode, and an equilibrium is reached after a time. The time taken to reach equilibrium depends *e.g.* on the nature of the adsorbate and of the adsorbent, the temperature the electrolyte concentration, the surface condition of the metal electrode, and its potential. By varying one parameter and keeping the others constant, one can obtain information about the nature and the kinetics of the adsorption[38].

The radioactive tracer method has become a valuable aid to the study of adsorption processes in organic electrochemistry. Thus *Hackermann et al.*[39] studied the adsorption of ^{14}C-labeled organic inhibitors in the corrosion of iron under stationary conditions. *Bockris et al.* have published investigations on the adsorption of organic substances (aldehydes, benzene, naphthalene, and *n*-decylamine) on platinum and partly also on gold and nickel[40]. They interpreted their results by a model of competitive adsorption of organic substances and of water.

8. Identification of Electrochemical Products by Mass Spectrometry

Any investigation of the kinetics of an electrode reaction must necessarily be incomplete until the intermediates and products have been definitely identified. The measuring methods described in the foregoing sections allow this identification only in exceptional cases, when the substances under investigation are present in the dissolved state (double-ring electrodes, electroluminescence, ESR spectroscopy). However, the reaction products are often adsorbed on the electrode. Their existence can be detected by optical methods, but identification has not been possible in the past.

Attempts have recently been made, therefore, to analyze adsorbed products of an electrode reaction in the mass spectrometer. *Bruckenstein*[41] used a microporous non-wetting electrode which is fitted as a cell wall with its hydrophobic side directly on the inlet part of a mass spectrometer (Fig. 31). Low molecular weight, readily volatizable reaction products are extracted from the electrode by the vacuum on the mass spectrometer side, and after ionization by electron impact they are subjected to mass analysis. Since the electrochemical cell is connected directly to the mass spectrometer, the product distribution can be measured as a function of the electrode potential, and the *m/e* signal can be measured as a function of time at a constant potential. Detailed information about the dependence of the reaction mechanism on the potential and about the strength of the adsorptive bond can be obtained in this way.

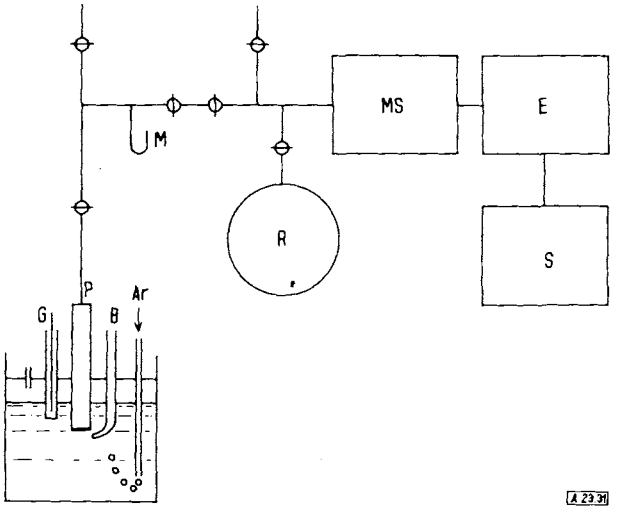


Fig. 31. Schematic representation of an apparatus for the direct analysis of electrochemical reaction products with the mass spectrometer (after [41]). B = reference electrode, E = electronics, G = counterelectrode, M = manometer, MS = mass spectrometer, P = porous electrode, R = reservoir, S = pen recorder.

Another mass-spectrometric method for the identification of adsorbed reaction products has been proposed by the present authors[42]. The electrode in this case is a metal foil 7 µm thick, which is etched at its lower edge. After the electrochemical reaction, this foil is placed in a mass spectrometer; the adsorbate is ionized by application of a very high electric field strength and detected in the mass analyzer. The field desorption method developed by *Beckey et al.*[43] has the special advantage that the molecular peak is normally the base peak. Since the starting substance and the reaction product are present together on the electrode, there is consequently only a slight overlap of the mass spectra, so that a definite identification of the desired substance is generally possible.

To demonstrate the applicability of the suggested method, the reaction product formed on anodic oxidation of 1-butanol in alkaline electrolyte at 700 mV_{RHE} was investigated.

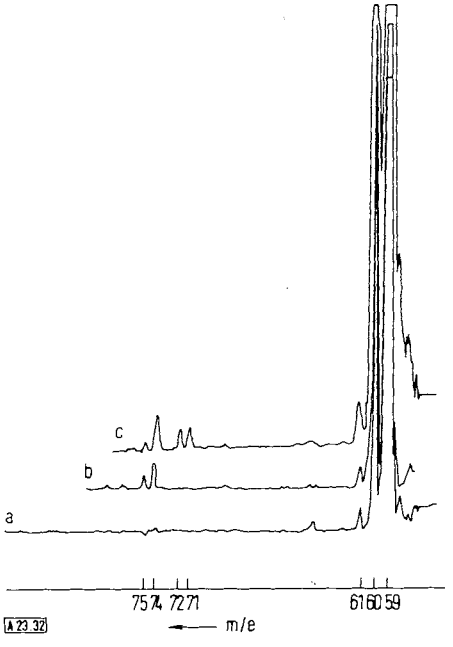


Fig. 32. Mass-spectrometric detection of the oxidation product of 1-butanol adsorbed on the electrode: a) Background spectrum and calibration spectrum of the platinum emitter used (calibrated with acetone, mass numbers 59, 60, and 61); b) mass spectrum of a solution of 0.473 M 1-butanol in 1 M KOH. The mass number 74 corresponds to the molecular peak of butanol (molecular weight 74.12); c) mass spectrum of the same solution as for b) after electrochemical oxidation of the butanol at +700 mV_{RHE}. The mass numbers 71 and 72 correspond to the oxidation product in question.

The results are shown in Fig. 32. Curve a shows the background spectrum of the mass spectrometer with the platinum foil described above as the emitter. The spectrum of acetone, which was used for calibration of the emitter in the mass spectrometer, can be seen at the right-hand edge of the diagram.

Curve b shows the same mass range as curve a. In this case the platinum foil was immersed in a solution of 1 M KOH + 0.473 M 1-butanol without application of a potential before it was placed in the mass spectrometer. The mass numbers 74 and 75 appear in the mass spectrum, 74 being the molecular peak of butanol (molecular wight 74.12).

Finally, before curve c was recorded, the butanol was electrochemically oxidized for about 30 s at a potential of 700 mV_{RHE}. In this case the mass spectrum contains the additional mass numbers 71 and 72, which correspond to the adsorbed oxidation product formed from the butanol by the elimination of hydrogen.

9. Outlook

Modern electrochemical methods nowadays make it possible to obtain accurate information about the kinetics of an electrode process. The rate-determining step of a reaction sequence can often be indicated, and the rate constants of preceding or subsequent chemical reactions can be measured with good accuracy. In establishing a reaction mechanism, however, the investigator must often resort to plausibility considerations, since the identification of the intermediates and frequently even of the end products of a reaction is possible only in exceptional cases.

It is not surprising, therefore, that the efforts of many electrochemists are being concentrated at present on the detection of intermediates. This progress report has shown the successes that have been achieved so far by the use of ESR spectroscopy and mass spectroscopy. It should be remembered, however, that ESR spectroscopy is confined to measurements on relatively long-lived free radicals in solution, mainly in organic solvents, and that mass spectroscopy can be used for the analysis only of practically stable products. There is as yet no sensitive *in-situ* method for the determination of short-lived intermediates on or in the vicinity of the electrode surface that would allow a rapid identification without influencing the course of the reaction.

It is clear that optical methods really offer the only possibility of further assistance here, and the first steps in this direction have already been taken. In the discussion of reflection spectroscopy and ellipsometry it was pointed out that variation of the wavelength of the incident light could yield information about the nature of the adsorbed substance. *Fleischmann et al.*[44] were recently able to identify surface layers by Raman spectroscopy with laser light sources. *Siegbahn et al.*[45] proposed the use of X-rays and electron diffraction.

The examples show that the development of optical methods into analytical procedures for electrochemically produced intermediates is being vigorously pursued at present. New impetus for the study of electrode kinetics may be expected from this quarter in the near future.

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Translated by Express Translation Service, London

[1] *F. G. Will* and *C. A. Knorr*, Z. Elektrochem. 64, 258, 270 (1960).

[2] *W. Vielstich*, Z. Instrumentenkunde 71, 29 (1963).

[3] *W. Vielstich*: Brennstoffelemente - Moderne Verfahren zur elektrochemischen Energiegewinnung. Verlag Chemie, Weinheim 1965.

[4] See ref. [3], p. 121.

[5] *B. D. Struck* and *W. Vielstich*, Electrochim. Acta 17, 1829 (1972).

[6] *W. Vielstich, U. Vogel, M. Kamal*, and *J. Mrha*, Entropie 32, 31 (1970).

[7] *M. W. Breiter*: Electrochemical Processes in Fuel Cells. Springer, Berlin 1969.

[8] *V. G. Levich*, Acta Physicochim. URSS 17, 257 (1942).

[9] *V. G. Levich*: Physicochemical Hydrodynamics. Prentice Hall, London 1962.

[10] *D. P. Gregory* and *A. C. Riddiford*, J. Chem. Soc. 1956, 3756.

[11] *G. Trimborn, A. Heindrichs*, and *W. Vielstich*, Messtechnik 9, 224 (1968).

[12] *B. Gostiša-Mihelčič, W. Vielstich*, and *A. Heindrichs*, Ber. Bunsenges. Phys. Chem. 76, 19 (1972).

[13] *D. Jahn* and *W. Vielstich*, J. Electrochem. Soc. 109, 849 (1962).

[14] *J. Koutecky* and *V. G. Levich*, Zh. Fiz. Khim. 32, 1556 (1958).

[15] *B. Gostiša-Mihelčič* and *W. Vielstich*, Ber. Bunsenges. Phys. Chem. 77, 476 (1973).

[16] *B. Miller, M. I. Bellavance, and S. Bruckenstein*, Anal. Chem. *44*, 1983 (1972).

[17] *C. H. Hamann* and *W. Vielstich*, J. Electroanal. Chem. *32*, 459 (1971).

[18] *W. J. Albery* and *S. Bruckenstein*, Trans. Faraday Soc. *62*, 1915, 1920 (1966).

[19] *G. Trimborn*, Dissertation, Universität Bonn 1969.

[20] *H. H. Bauer, D. L. Smith*, and *P. J. Elving*, J. Amer. Chem. Soc. *82*, 2094 (1960).

[21] *B. Breyer* and *H. H. Bauer*: Alternating Current Polarography and Tensametry. Wiley, New York 1963.

[22] *R. Neeb*, Z. Anal. Chem. *188*, 401 (1962).

[23] *H. Gerischer*, Z. Elektrochem. *58*, 9 (1954).

[24] *D. E. Smith*, Electroanal. Chem. *1*, 1 (1966).

[25] *J. W. Strojek* and *T. Kuwana*, J. Electroanal. Chem. *16*, 471 (1968).

[26] *W. N. Hansen, T. Kuwana*, and *R. A. Osteryoung*, J. Amer. Chem. Soc. *88*, 1062 (1966).

[27] *B. S. Pons, J. S. Mattson, L. O. Winstroem*, and *H. B. Mark, Jr.*, Anal. Chem. *39*, 685 (1967).

[28] *A. H. Reed* and *E. Yeager*, 19th CITCE Conference, Detroit 1968, paper 308 (Extended Abstracts p. 195).

[29] *A. H. Reed* and *E. Yeager*, Appl. Opt. *7*, 451 (1968).

[30] *W. J. Plieth*, Chem. Ing. Tech. *44*, 221 (1972).

[31] *T. Takamura, K. Takamura, W. Nippe*, and *E. Yeager*, 135th National Meeting, The Electrochem. Soc., New York 1969 (Extended Abstracts p. 388).

[32] *F. Gorn* and *K. J. Vetter*, Z. Phys. Chem. NF *77*, 317 (1972).

[33] *A. K. N. Reddy, M. Genshaw*, and *J. O'M. Bockris*, J. Electroanal. Chem. *8*, 406 (1964).

[34] *A. K. N. Reddy, M. G. B. Rao*, and *J. O'M. Bockris*, J. Chem. Phys. *42*, 2246 (1965).

[35] *J. L. Ord* and *D. J. DeSmet*, J. Electrochem. Soc. *113*, 1258 (1966).

[36] *T. Kuwana*, Electroanal. Chem. *1*, 157 (1966).

[37] *B. Kastening*, Chem. Ing. Tech. *42*, 190 (1970).

[38] *N. A. Balashova* and *V. E. Kazarinov*, Electroanal. Chem. *3*, 135 (1969).

[39] *I. Bordeaux* and *N. Hackermann*, J. Phys. Chem. *61*, 1323 (1957).

[40] See, *e.g., J. O'M. Bockris* and *D. A. Swinkles*, J. Electrochem. Soc. *111*, 736 (1964).

[41] *S. Bruckenstein* and *J. Comeau*, Diss. Faraday Soc., in press.

[42] *J. Heitbaum* and *W. Vielstich*, to be published.

[43] *H. D. Beckey*: Field Ionisation Mass Spectrometry. Pergamon, Oxford 1971; Angew. Chem. *81*, 662 (1969); Angew. Chem. internat. Edit. *8*, 623 (1969).

[44] *M. Fleischmann, P. J. Hendra*, and *A. J. McQuillan*, J. C. S. Chem. Comm. *1973*, 80.

[45] *U. Gelius, E. Basilier, S. Svenson, T. Bergmark*, and *K. Siegbahn*, Comm. of the Uppsala University UUIP-817, April 1973.

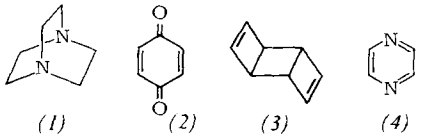
Effects of Through-Bond Interaction

By Rolf Gleiter[*]

The effect of through-bond interaction is derived for 1,4-butanediyl as an example, and changes caused by this effect in the ground state of the system are demonstrated. Spectroscopic methods for the detection of the effect are discussed, and its chemical consequences are illustrated by a number of examples.

1. Introduction

Until a few years ago the interaction of lone pairs of electrons and of π orbitals situated more than 3 Å apart was assumed to be very small. Examples of this situation are found in 1,4-diazabicyclo[2.2.2]octane *(1)*, *p*-benzoquinone *(2)*, *anti*-tricyclo[4.2.0.0^{2,5}]octa-3,7-diene *(3)*, and pyrazine *(4)*. The

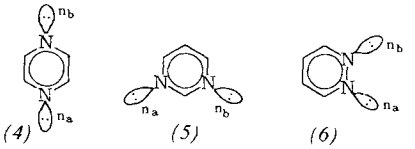


(1) *(2)* *(3)* *(4)*

assumption that these interactions are very small became the subject of critical examination following calculations by *Hoffmann et al.* for the three isomeric diazabenzenes[1] and didehydrobenzenes[2]. These calculations were stimulated by experiments by *Rees* and *Storr*[3] on cycloadditions to 1,8-didehydronaphthalene (1,8-naphthalenediyl) and by investigations by *McKinney* and *Geske*[4] on the radical-cation $(1)^+$.

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The results of these calculations will be illustrated for the three diazabenzenes (diazines) pyrazine *(4)*, pyrimidine *(5)*, and pyridazine *(6)*. If the two orbitals indicated on the nitrogen



(4) *(5)* *(6)*

atoms in *(4)*, *(5)*, and *(6)* are denoted by n_a and n_b, we can write down the two non-normalized, but symmetry-adapted linear combinations

$$n_+ = (n_a + n_b)$$
$$n_- = (n_a - n_b)$$

which are shown schematically in Figure 1. The n_+ linear combination is symmetric (S) and the n_- linear combination antisymmetric (A) with respect to the mirror plane m.

If the interaction between n_a and n_b is very small, n_+ and n_- should have approximately equal energies (Fig. 2, center). If the interaction is large, on the other hand, the energy

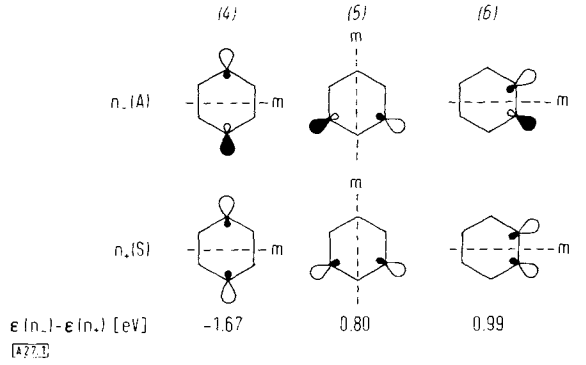


Fig. 1. Schematic representation of the linear combinations of the non-bonding orbitals n_a and n_b for the diazabenzenes *(4)*–*(6)*.

levels belonging to n_+ and n_- should be very different (Fig. 2, right and left). In the latter case there are two conceivable possibilities: Either n_+ is lower on the energy scale than n_- (Fig. 2, right) or *vice versa* (Fig. 2, left).

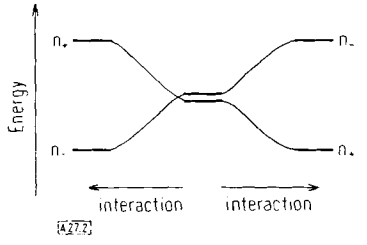


Fig. 2. Variation of the energy levels of n_+ and n_- as a function of the interaction between n_a and n_b.

Surprisingly, the EH (extended Hückel) calculations[5] for the diazabenzenes and the didehydrobenzenes not only indicated a large difference (about 1.5 eV) for the compounds of the type *(4)*, but also showed that n_+ is above n_- in this case, whereas n_+ is below n_- for compounds of the types *(5)* and *(6)*. The calculated orbital energy differences $\varepsilon(n_-)-\varepsilon(n_+)$ are given at the bottom of Figure 1.

The discovery that the n_+ level can be either lower or higher than the n_- level suggested the existence of two interaction mechanisms, *i.e.* a purely spatial interaction[*] (through space), in which the n_+ level falls below the n_- level, and an interaction mechanism in which the σ skeleton (through bond) leads, under certain conditions[**], to a reversal of this "normal" sequence.

2. Theory of Through-Bond Interaction

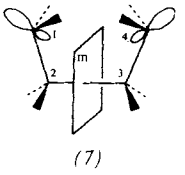
The purely spatial interaction is described in detail in textbooks on chemical bonding. The effect of through-bond interaction will be discussed below for the case of 1,4-butanediyl *(7)*. For a detailed theoretical treatment the reader is referred to the literature[2a].

Just as for the n orbitals of the diazabenzenes *(4)*, *(5)*, and *(6)*, we can form the two symmetry-adapted linear combinations $n_+(S)=(n_1+n_4)$ and $n_-(A)=(n_1-n_4)$ for the orbitals n_1 and n_4 shown on the centers C^1 and C^4 in *(7)*. If one considers only the spatial interaction, the energy difference between n_+ and n_- in *(7)* should be small (Fig. 3, left).

[*] The simplest interaction of this type is that of two H(1s) orbitals leading to the MOs of hydrogen [6, 7].

[**] For a through-bond interaction *via* an odd number of σ bonds, the n_- level is always below the n_+ level [2a].

This energy difference depends on the overlap integral $\langle n_1|n_4\rangle$, which is small because of the spatial separation of the two centers (about 3 Å).



(7)

However, relatively strong splitting can be achieved for n_+ and n_- through the interaction with the σ and σ^* orbitals of the C^2—C^3 bond. As can be seen from Figure 3, the σ orbital is symmetric (S) and the σ^* orbital antisymmetric (A) with respect to the mirror plane m in *(7)*. The interaction of the other orbitals in *(7)* with n_+ and n_- may be disregarded to a first approximation[2a][*].

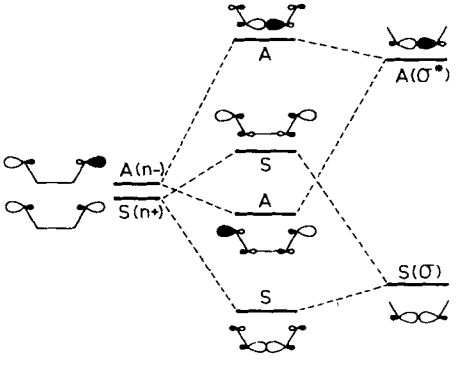


Fig. 3. Interaction diagram for the orbitals of the centers C^1 and C^4 and of the C^2—C^3 σ bond in 1,4-butanediyl *(7)*.

Qualitative rules derived from perturbation theory[7][**] were used to construct the interaction diagram shown in Figure 3 for the σ and n levels.

It can be seen from Figure 3 that n_+ is destabilized by the interaction with the σ orbital, whereas n_- is stabilized by the interaction with the σ^* orbital.

Figure 4 shows a comparison of the one-electron orbitals from an EH calculation for 1,4-butanediyl with and without through-bond interaction; the MO scheme for a through-bond interaction is also compared with the π-MO scheme of 1,3-butadiene.

This diagram leads to three conclusions for a system in which only the two lowest MOs are occupied:

1) The through-bond interaction leads to the reversal of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) compared with a system in which this interaction is absent (Fig. 4, left).

2) The system with through-bond interaction is more stable than the system without this interaction[***].

[*] Apart from the C^2—C^3 bond, all other bonds (*e.g.* C^1—C^2 and C^3—C^4) give symmetric *and* antisymmetric combinations of σ orbitals and σ^* orbitals. It may be assumed to a first approximation that the position *e.g.* of the n_- level does not change if one symmetric orbital is lower (σ) and one is higher (σ^*).

[**] These rules are:
Only orbitals of the same symmetry interact with one another. Interacting non-degenerate orbitals "repel" each other, *i.e.* the lower orbital on the energy scale is stabilized, while the higher one is destabilized.

[***] In our example the total energy of the system is $E=\Sigma n_i\varepsilon_i$. n_i is the occupancy and ε_i is the orbital energy. In the dianion of *(7)*, 1,4-butanediide $(7)^{2-}$, the through-bond interaction would lead to less stabilization than in *(7)*.

3) The C^2—C^3 bond in *(7)* is weakened by a through-bond interaction.

The first two conclusions require no further explanation, but the third will be briefly interpreted. The predicted bond alternance (bonds C^1—C^2 and C^3—C^4 stronger than C^2—C^3) can be best understood by comparison of the MO scheme for *(7)* (Fig. 4, center) with the π-MO scheme for 1,3-butadiene (Fig. 4, right). The one-electron MO schemes are identical as to the symmetry of the orbitals with respect to the mirror plane m. In both cases an S orbital and an A orbital are

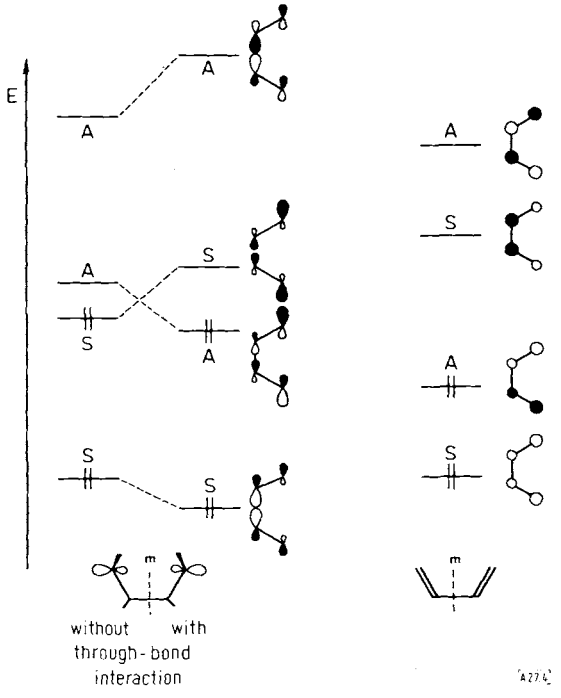


Fig. 4. Comparison of the orbital energies of a system with and without through-bond interaction with the π-MOs of 1,3-butadiene.

each occupied by two electrons. Because of the occupation of the lowest A orbital, which has a node between the centers C^2 and C^3, the contribution of the lowest occupied S orbital to the bond order is roughly cancelled out. In 1,3-butadiene the result is a weakening of the π bonding between the centers C^2 and C^3 (single bond) and a strengthening of the π bonding between the centers C^1 and C^2 and between C^3 and C^4 (double bond).

The same is true of *(7)*, since here again only one S orbital and one A orbital are occupied. These qualitative deductions

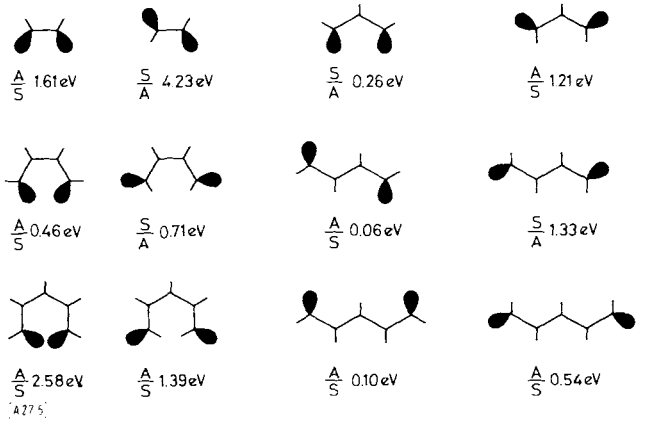


Fig. 5. Model arrangements of lone pairs of electrons und σ bonds. The symmetry of LUMO and HOMO and the calculated energy difference between these two orbitals are indicated under each formula.

have been confirmed by EH calculations[8, 9]. Thus as soon as through-bond interaction predominates, *i.e.* A is lower than S, the C^2—C^3 bond is distinctly weakened in comparison with C^1—C^2 and C^3—C^4.

Conclusions 2 and 3 disappear for a system in which the three lowest orbitals are occupied. Examples of such systems would be 1,4-butanediide $(7)^{2-}$ and 1,2-diaminoethane.

The model calculations by *Hoffmann et al.*[2a] that were mentioned in the introduction have also been carried out for other systems (Fig. 5). The order LUMO-HOMO and the energy difference between the two orbitals are indicated under the corresponding formulas in Figure 5.

3. Methods of Detecting Through-Bond Interaction

Among the many possible MO descriptions of the bonding in 1,4-butanediide $(7)^{2+}$ and in the isoelectronic 1,2-diaminoethane *(8)*, two are outstanding; these are the canonical MOs shown schematically in Figures 3 and 4 and the equivalent MOs. The latter are approximately localized in the bonds or lone pairs of electrons (see below). The two descriptions give the same total energy for the system, but different orbital energies[6][*].

$$^{\ominus}\ddot{C}H_2-CH_2-CH_2-\ddot{C}H_2^{\ominus} \qquad (7)^{2-}$$

$$H_2\ddot{N}-CH_2-CH_2-\ddot{N}H_2 \qquad (8)$$

In the case of ionization (*e.g.* $(8)^+$) or excitation (*e.g.* $(8)^*$) or interaction with another system (X) (*e.g.* $(8)\cdots X$), localized MOs are no longer suitable for their description.

If we wish to "detect" the orbital sequence as expected for the canonical MO description, therefore, we must introduce a perturbation in the manner indicated above. An indication of the correctness of the derived orbital schemes should be obtainable from photoelectron (PE) spectra, ESR spectra, charge transfer spectra, pK_a values, *etc.*

3.1. PE Spectroscopy[10][**]

n-Orbital splitting of 2.13[11] and 1.72 eV[12] is in fact found for the compounds *(1)* and *(4)* respectively; this agrees well with semiempirical[1, 12, 14–16] and *ab-initio* calculations[13]. By analysis of the vibrational fine structure of the first two bands in the PE spectrum of *(1)*, it has been shown[17] that the level corresponding to the first band on ionization belongs to the n_+ orbital, and that of the second band to the n_- orbital. The PE spectrum of *(4)* also showed[18] that the n_+ level is higher than the n_- level. As in the case of the diazines, through-bond interaction effects can also be detected for the diazanaphthalenes[19].

The prediction[20] of a through-bond interaction between the 2p orbitals of α,β-dicarbonyl compounds has also been confirmed by PE spectroscopy[21, 22]. As in the examples considered above, it is found experimentally here again that the n_+ linear combination is above the n_- combination (cf. Fig. 6). Another point that seems interesting is that the splitting $\Delta n = |n_+ - n_-|$ is practically independent of the dihedral angle

[*] The total energy is an observable, whereas the orbital energy is not.

[**] Photoelectron spectroscopy measures transition from the ground state to the ionized state. Measurements of this type therefore only provide information about how the system reacts to the removal of an electron.

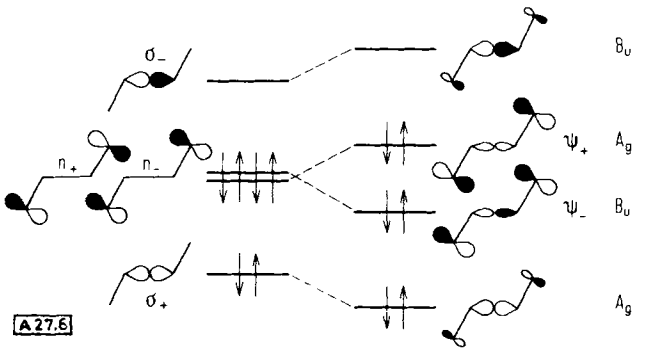


Fig. 6. Schematic representation of through-bond interaction between the linear combinations n_+ and n_- in *trans*-glyoxal (symmetry C_{2h}).

θ of the two carbonyl groups. Thus the splitting is 1.9 eV for biacetyl (θ = 180 °C) and 1.6 eV for camphorquinone (θ = 0°). The through-bond interaction between π orbitals in γ,δ-unsaturated ketones[23] and 1,4-dienes has been demonstrated by many examples[24–27]. In *syn*-tricyclo[4.2.0.0^{2,5}]octa-3,7-diene[25] and in hypostrophene (tetracyclo[5.3.0.0^{2,6}.0^{3,10}]-deca-4,8-diene)[26], for example, it leads to reversal of the orbital sequence (A below S) from the through-space interaction[*].

3.2. Electronic Spectroscopy

From what has been said so far it is easy to understand that through-bond interaction can also be detected by electronic spectroscopy. The electronic spectra of γ,δ-unsaturated ketones and amines show the existence of an interaction between the two chromophores when the conformation of the molecule allows an interaction *via* the σ skeleton[28]. The electronic spectra of the diazanaphthalenes[29], of pyrazine[29, 30], and of dimethylpyrazine[30, 31] can be plausibly interpreted by the concept of through-bond interaction. Without this interaction, no splitting would be expected for $\pi^* \leftarrow n_A$ and $\pi^* \leftarrow n_S$ in pyrazine and 1,4-diazanaphthalene, whereas values between 0.2 and 0.5 eV are found. This interpretation of the spectra is supported by *ab-initio*[32] and semiempirical calculations[16, 30, 33, 34].

Similar conclusions can be drawn for the α,β-dicarbonyl compounds. The observed splitting of the two $\pi^* \leftarrow n$ transitions for biacetyl is 1.36 eV[35, 36], and the energy difference between n_S and n_A as found from the PE spectra is 1.9 eV[21][**].

3.3. Other Investigations

One important result of the through-bond interaction concept is the prediction that n_+ is strongly delocalized. This prediction is confirmed by susceptibility measurements on the three diazabenzenes[37]. H—D exchange reactions on pyridine, the diazabenzenes, and the diazanaphthalenes[38], on the other hand, give no indication of a through-bond interaction. This is also true of basicity measurements on 1-azabicyclo[2.2.2]octane and *(1)*[39] and of the diazabenzene-catalyzed hydrolysis of 2,4-dinitrophenyl acetate[40][***].

[*] This orbital sequence could be the reason why the compounds do not undergo intramolecular cyclization on irradiation.

[**] The splitting ΔE of the two $\pi^* \leftarrow n$ transitions as calculated from the ionization potential of biacetyl and an estimation [30] of the Coulomb and exchange integrals by the CNDO/2 method is − 1.6 eV.

[***] The systems investigated are all derived from $(7)^{2-}$ or *(8)*. The perturbation introduced is very slight in comparison with electronic excitation or ionization.

4. Consequences for the Ground State and for Reactivity

4.1. Fragmentation

A typical result of the bond weakening predicted as the third conclusion in Section 2 is heterolytic fragmentation, which was studied in detail by *Grob et al.*[41].

$$a\text{–}b\text{–}c\text{–}d\text{–}x \longrightarrow a\text{–}b + c{=}d + x: \qquad (1)$$

An example of this is the fragmentation of γ-amino-halo compounds into olefins and imonium salts.

$$R_2N\text{–}C^3H_2\text{–}C^2H_2\text{–}C^1H_2\text{–}X \longrightarrow R_2\overset{\oplus}{N}{=}CH_2 + CH_2{=}CH_2 + X^{\ominus} \qquad (2)$$

This reaction can proceed either by a concerted mechanism or as a two-step process. In the concerted mechanism the C^2—C^3 and C^1—X bonds are broken simultaneously. In the two-step process the C^1—X bond first heterolyzes, with formation of the cation $R_2\overset{\oplus}{N}$—CH_2—CH_2—$\overset{\oplus}{C}H_2$, which is isoelectronic with *(7)*.

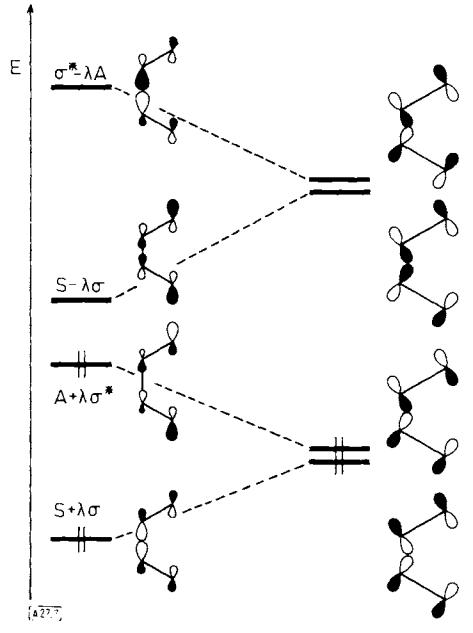
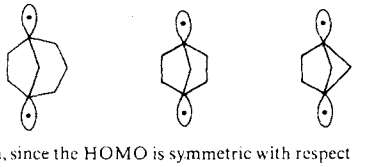


Fig. 7. Correlation diagram for the fragmentation of 1,4-butanediyl *(7)* into two ethylene molecules.

As soon as the through-bond interaction dominates in this cation, the C^2—C^3 bond should be weakened, and the species can undergo fragmentation. A necessary condition[9] for a fragmentation is that the orbital A (HOMO) should be lower than S (LUMO); then and only then is the fragmentation allowed[43] (cf. Fig. 7). The steric condition[41] for this is generally[*] the antiperiplanar arrangement of the lone pair, the C^2—C^3 σ bond, and the unoccupied 2p orbital on C^1.

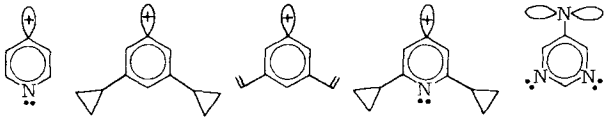
[*] According to an EH calculation [42], the biradicals



should *not* undergo fragmentation, since the HOMO is symmetric with respect to the plane of symmetry. However, the steric condition [41] for a fragmentation is satisfied.

4.2. Possibilities of Stabilization

It follows from the second conclusion in Section 2 that the effect of the through-bond interaction can be used for stabilization. This can be illustrated by predictions on the stabilization of the phenyl cation[44]. According to EH calculations, the aryl cations *(9)*—*(12)*, for example, should be 0.1—0.5 eV more stable than the phenyl cation.

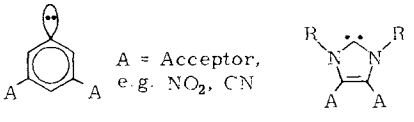


(9) *(10)* *(11)* *(12)* *(13)*

In these compounds an interaction between the positive center (low unoccupied orbital) and the lone pair on the nitrogen (*(9)*, *(12)*), the Walsh orbitals of the three-membered rings (*(10)*, *(12)*), or the π orbitals of the double bonds (*(11)*), which are perpendicular to the plane of the ring, should lead to stabilization.

In 5-pyrimidinylnitrene *(13)*, the singlet state (π^2) should be stabilized in relation to the triplet state by the through-bond interaction between the lone pairs on the ring nitrogen atoms and the empty 2p orbital on the nitrene nitrogen.

Just as a positive charge can be stabilized by donor groups (high occupied orbitals), so acceptor groups (low unoccupied orbitals) can stabilize a carbanion. Examples of this are the *m*-nitrophenyl anion *(14)*[45] and the carbene *(15)*. In the latter compound, the singlet state (σ^2) should be stabilized in relation to the triplet state (σp) by a through-bond interaction.



(14) *(15)*

4.3. Other Examples

An example of the course of a reaction being influenced by through-bond interaction is provided by the photolysis of four-membered ring ketones[46]. In this reaction the light-induced ring expansion to form the isomeric tetrahydro-2-furylidene, which is not observed for homologous cycloalkanones, has been explained by through-bond interaction.

The high stereospecificity of the cycloaddition of enol ethers to tetracyanoethylene *via* 1,4-dipoles[47] is also attributable to the domination of a through-bond interaction in the 1,4-dipole[48].

5. Outlook

The concept of through-bond interaction was recognized six years ago by *Hoffmann et al.*[2a]. Apart from theoretical investigations, which demonstrated the consequences of this new concept for chemical reactions, it has been mainly photoelectron spectroscopy that has shown that through-bond interaction effects can be very considerable. Besides further examples of the existence of a through-bond interaction in formal 1,4-diradicals and 1,4-dipoles, in electronic transitions, and in ionization, further investigations on systems derived from $(7)^{2-}$, but in which the perturbation does not lead to ionization or electronic excitation, appear to be particularly interesting. On the theoretical side, the study of the interactions that were disregarded as a first approximation in the model *(7)* could lead to new results.

I am very grateful to Professor Roald Hoffmann and Professor Edgar Heilbronner, with whom I had the pleasure of working on through-bond interaction effects.

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[1] *R. Hoffmann*, J. Chem. Phys. 40, 2745 (1964); *W. Adam, A. Grimison*, and *R. Hoffmann*, J. Amer. Chem. Soc. 91, 2590 (1969).

[2] a) *R. Hoffmann, A. Imamura*, and *W. J. Hehre*, J. Amer. Chem. Soc. 90, 1499 (1968); b) *R. Hoffmann*, Accounts Chem. Res. 4, 1 (1971); c) *R. Hoffmann* and *W.-D. Stohrer*, Spec. Lect. XXIIIrd Int. Congr. Pure Appl. Chem., Vol. 1, p. 157. Butterworths, London 1971.

[3] *C. W. Rees* and *R. C. Storr*, Chem. Commun. 1965, 193.

[4] *T. M. McKinney* and *D. H. Geske*, J. Amer. Chem. Soc. 87, 3013 (1965).

[5] *R. Hoffmann*, J. Chem. Phys. 39, 1397 (1963); *R. Hoffmann* and *W. N. Lipscomb*, *ibid.* 36, 2179, 3489 (1962); 37, 2877 (1962).

[6] *W. Kutzelnigg*, Angew. Chem. 85, 551 (1973); Angew. Chem. internat. Edit. 12, 546 (1973).

[7] *E. Heilbronner* and *H. Bock*: Das HMO-Modell und seine Anwendung. Vol. 1. Verlag Chemie, Weinheim 1968; *M. J. S. Dewar*: The Molecular Orbital Theory of Organic Chemistry. McGraw-Hill, New York 1969.

[8] *R. Hoffmann, S. Swaminathan, B. G. Odell*, and *R. Gleiter*, J. Amer. Chem. Soc. 92, 7091 (1970).

[9] *R. Gleiter, W.-D. Stohrer*, and *R. Hoffmann*, Helv. Chim. Acta 55, 893 (1972).

[10] Reviews: *H. Bock* and *B. G. Ramsey*, Angew. Chem. 85, 773 (1973); Angew. Chem. internat. Edit. 12, 734 (1973); *D. W. Turner, C. Baker, A. D. Baker*, and *C. R. Brundle*: Molecular Photoelectron Spectroscopy. Wiley-Interscience, London 1970; *S. D. Worley*, Chem. Rev. 71, 295 (1971).

[11] *P. Bischof, J. A. Hashmall, E. Heilbronner*, and *V. Hornung*, Tetrahedron Lett. 1969, 4025; *Y. Hamada, A. Y. Hirakawa, M. Tsuboi*, and *H. Ogata*, Bull. Chem. Soc. Jap. 46, 2244 (1973).

[12] *R. Gleiter, E. Heilbronner*, and *V. Hornung*, Helv. Chim. Acta 55, 255 (1972); Angew. Chem. 82, 878 (1970); Angew. Chem. internat. Edit. 9, 901 (1970); *C. Fridh, L. Asbrink, B. Ö. Jonsson*, and *E. Lindholm*, Int. J. Mass Spectrom. Ion Phys. 8, 101 (1972); references cited therein.

[13] *E. Clementi*, J. Chem. Phys. 46, 4737 (1967); *J. Almlöf, B. Roos, U. Wahlgren*, and *H. Johansen*, J. Electron Spectrosc. Rel. Phen. 2, 51 (1973); *M. H. Palmer, A. J. Gaskell*, and *R. H. Findlay*, Tetrahedron Lett. 1973, 4659.

[14] *J. Spanget-Larsen*, J. Electron Spectrosc. Rel. Phen. 2, 33 (1973).

[15] *I. Fischer-Hjalmars* and *M. Sundbom*, Acta Chem. Scand. 22, 607 (1968).

[16] *M. Sundbom*, Acta Chem. Scand. 25, 487 (1971).

[17] *E. Heilbronner* and *K. A. Muszkat*, J. Amer. Chem. Soc. 92, 3818 (1970).

[18] *K. A. Muszkat* and *J. Schäublin*, Chem. Phys. Lett. 13, 301 (1972).

[19] *F. Brogli, E. Heilbronner*, and *T. Kobayashi*, Helv. Chim. Acta 55, 274 (1972); *D. M. W. van den Ham* and *D. van der Meer*, J. Electron Spectrosc. Rel. Phen. 2, 247 (1973); Chem. Phys. Lett. 15, 549 (1972).

[20] *J. R. Swenson* and *R. Hoffmann*, Helv. Chim. Acta 53, 2331 (1970).

[21] *D. O. Cowan, R. Gleiter, J. A. Hashmall, E. Heilbronner*, and *V. Hornung*, Angew. Chem. 83, 405 (1971); Angew. Chem. internat. Edit. 10, 401 (1971); *J. Kelder, H. Cerfontain, B. R. Higginson*, and *D. R. Lloyd*, Tetrahedron Lett. 1974, 739.

[22] *J. Kroner* and *W. Strack*, Angew. Chem. 84, 210 (1972); Angew. Chem. internat. Edit. 11, 220 (1972).

[23] *M. D. Brown, J. Hudec*, and *J. M. Mellor*, Chem. Commun. 1971, 1640.

[24] R. Hoffmann, E. Heilbronner, and R. Gleiter, J. Amer. Chem. Soc. 92, 706 (1970).

[25] R. Gleiter, E. Heilbronner, M. Hekman, and H. D. Martin, Chem. Ber. 106, 28 (1973).

[26] W. Schmidt and B. I. Wilkins, Tetrahedron 28, 5649 (1972).

[27] K. W. Shen and N. A. Kuebler, Tetrahedron Lett. 1973, 2145.

[28] R. C. Cookson, J. Henstock, and J. Hudec, J. Amer. Chem. Soc. 88, 1060 (1966); J. Hudec, Chem. Commun. 1970, 829; J. Kuthan, J. Pleček, and L. Musil, Collect. Czech. Chem. Commun. 39, 720 (1974).

[29] A. D. Jordan, I. G. Ross, R. Hoffmann, J. R. Swenson, and R. Gleiter, Chem. Phys. Lett. 10, 572 (1971).

[30] E. Haselbach, Z. Lanyiova, and M. Rossi, Helv. Chim. Acta 56, 2889 (1973).

[31] W. R. Moomaw, M. R. Decamp, and P. C. Podore, Chem. Phys. Lett. 14, 255 (1972).

[32] M. Hackmeyer and J. W. Whitten, J. Chem. Phys. 54, 3739 (1971).

[33] T. Yonezawa, H. Kato, and H. Kato, Theor. Chim. Acta 13, 125 (1969).

[34] R. L. Ellis, G. Kuehnlenz, and H. H. Jaffé, Theor. Chim. Acta 26, 131 (1972).

[35] N. J. Leonhard, H. A. Laitnien, and E. H. Mottus, J. Amer. Chem. Soc. 75, 3300 (1953).

[36] J. N. Murrell: Elektronenspektren organischer Moleküle. Bibliographisches Institut, Mannheim 1967, pp. 194ff. and further references cited therein.

[37] J. D. Wilson, J. Chem. Phys. 53, 467 (1970).

[38] J. A. Zoltewicz, G. Grahe, and C. L. Smith, J. Amer. Chem. Soc. 91, 5501 (1969); J. A. Zoltewicz and A. A. Sale, ibid. 95, 3928 (1973).

[39] R. H. Staley and J. L. Beauchamp, J. Amer. Chem. Soc. 96, 1604 (1974).

[40] J. A. Zoltewicz and H. L. Jacobson, Tetrahedron Lett. 1972, 189.

[41] Reviews: C. A. Grob, Experientia 13, 126 (1957); Theoretical Organic Chemistry, Report on the Kekulé Symposium, Butterworths, London 1958, p. 114; Bull. Soc. Chim. Fr. 1960, 1360; C. A. Grob and P. W. Schiess, Angew. Chem. 79, 1 (1967); Angew. Chem. internat. Edit. 6, 1 (1967); C. A. Grob, ibid. 81, 543 (1969) and 8, 535 (1969), respectively.

[42] W.-D. Stohrer and R. Hoffmann, J. Amer. Chem. Soc. 94, 779 (1972).

[43] R. B. Woodward and R. Hoffmann, Angew. Chem. 81, 797 (1969); Angew. Chem. internat. Edit. 8, 781 (1969).

[44] R. Gleiter, R. Hoffmann, and W.-D. Stohrer, Chem. Ber. 105, 8 (1972).

[45] P. Buck, R. Gleiter, and G. Köbrich, Chem. Ber. 103, 1431 (1970).

[46] G. Quinkert, P. Jacobs, and W.-D. Stohrer, Angew. Chem. 86, 197 (1974); Angew. Chem. internat. Edit. 13, 197 (1974); W.-D. Stohrer, G. Wiech, and G. Quinkert, ibid. 86, 199 (1974) and 13, 199 (1974), respectively; W.-D. Stohrer, P. Jacobs, K. H. Kaiser, G. Wiech, and G. Quinkert, Fortschr. Chem. Forsch. 46, 181 (1974).

[47] R. Huisgen, R. Schug, and G. Steiner, Angew. Chem. 86, 48 (1974); Angew. Chem. internat. Edit. 13, 81 (1974).

[48] P. Hofmann and R. Gleiter, Tetrahedron Lett., in press.

Prescriptions and Ingredients for Controlled CC Bond Formation with Organometallic Reagents

New synthetic methods (5)

By Manfred Schlosser[*]

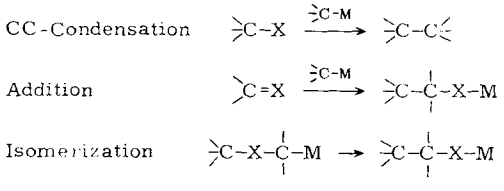
Merits and drawbacks of known carbon-carbon linking procedures are outlined. Two novel methods are discussed in some detail: the copper-catalyzed alkylation of Grignard reagents and reactions with allylpotassium compounds. Both methods provide a very efficient access to saturated, unsaturated, as well as functionally substituted hydrocarbons and moreover permit an astonishing degree of regio- and stereoselective control of olefin synthesis.

1. Introduction

"The synthesis of most organic molecules can be broken down into the problems of preparing the carbon framework and that of the introduction, modification and (or) removal of various functional groups"[1]. If we accept this approach, then the formation of the carbon skeleton is generally the more demanding part of the task. Fortunately, we can draw on a large repertoire of diverse methods for its accomplishment, though very few are without complications or of universal application. The development of new methods and the improvement of known ones, and the extension of their scope, will continue to tax the ingenuity of the synthetic chemist for a long time to come.

2. Possibilities of CC Bond Formation with Organometallic Reagents

As in the past, organometallic chemistry will continue to play an important role in the further evolution of developments in this field. How can its contribution be defined, and what inherent advantages does it offer? Let us first consider the various types of pertinent reactions. They can be roughly divided into three groups[2, 3]:



Rearrangements offer a most convenient, but insufficiently exploited route for linking two carbon atoms. Numerous syntheses of cyclic[4, 5] and open-chain[6] compounds have utilized this principle.

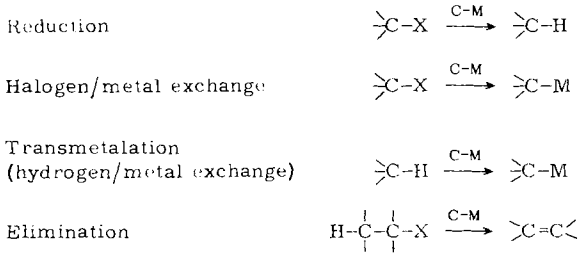
Examples of *additions* of carbanionic species to aldehydes, ketones, and carbon dioxide are too numerous to list. Generally trouble-free, these reactions are nevertheless occasionally accompanied by side reactions, especially reduction of the CO double bond by hydrogenation, particularly when there is massive steric hindrance of the carbonyl group. In contrast, carbon monoxide combines only reluctantly with organo-alkali (and alkaline earth) metals to form a mixture of products[2]; however, its fixation to acetylenes, olefins, or allyl halides can be readily

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effected with transition element complexes[7]. The most popular and versatile method for the directed formation of CC double bonds, the Wittig reaction[8-9], also belongs to this class of carbonyl additions.

Organometallic additions to CC double and triple bonds that proceed smoothly are less common. A refreshing exception is found in the highly predictable copper-catalyzed additions of organomagnesium compounds to the vinylogous position of an α,β-unsaturated ketone or ester (1,4 additions; cf. ref.[21]), which are of immense preparative value. However, other variants are too readily overshadowed by competitive reactions (*e.g.* metalations), or they continuously recur and thus evolve into polymerizations. These undesirable effects can frequently be avoided by base-catalyzed formation of the organometallic compound *in situ* from a suitable hydrocarbon in the presence of an olefin[10].

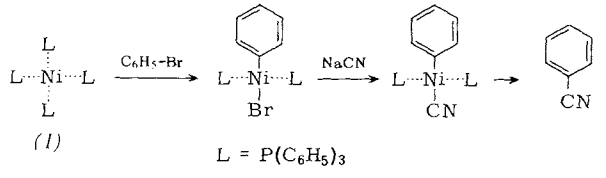
The picture is even less clear-cut when we turn to the many methods for CC bond-formation *via condensation reactions*. Based on the analogy of nucleophilic substitution these condensations should take place without difficulty when an organometallic reagent is allowed to react with an alkyl halide (or alkyl *p*-toluenesulfonate). However, the reaction is notoriously prone to go off course. In a radical process the halogen may get lost and be replaced by hydrogen; alternatively, the halogen and the metal in the reactant can exchange places; unless the organometallic compound prefers to exchange metal for hydrogen, that is to metalate an acidic CH bond of the electrophilic substrate; finally, hydrogen and halogen may be lost simultaneously by β-elimination[2,3]:



Attempts to force the desired condensation by employing a stronger reagent are doomed to failure. Any predominance of secondary reactions with Grignard reagents is merely enhanced on use of lithium derivatives and even more so with potassium derivatives, for an increase in the carbanion character of an organometallic species—whether caused by a more electropositive metal or by a solvent with higher solvating power—will invariably promote hydrogen/metal exchange at the expense of other possible reactions[3]. The reagents of choice are therefore organometallic compounds with high nucleophilicity but low basicity. Such properties are available in two cases: either in compounds of transition elements, or in resonance-stabilized alkali metal derivatives. The following two sections contain typical examples illustrating both approaches.

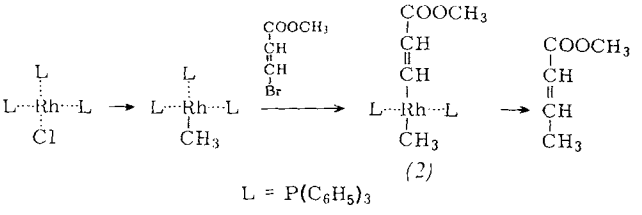
3. Organocopper Reagents

Compounds of transition elements, such as the Ni^0 complex *(1)*[11], resemble the carbenes or, more precisely, carbene precursors (carbenoids *etc.*) in certain respects. Since the weakly bound ligands are easily removed, the central atom displays markedly electrophilic character. On the other hand it also possesses lone pairs in an outer shell[*]. Like carbenes, they can therefore exhibit both electron-donor and electron-acceptor properties, *e.g.* on insertion into carbon-halogen bonds. If a nucleophilic carbon component then also approaches the metal, the unstable intermediate complex can rapidly decompose[12]. Without abandoning contact with the metal, the valences of the two carbon atoms directed toward the central atom glide toward one another until the new CC bond is completely formed. It is thus possible to largely retain the structure[13] and the configuration[14] of the condensation partners.



(1)

In the majority of reaction sequences of this type, however, the nucleophilic component is first fixed to the transition metal (*e.g.* rhodium)[15], and the electrophilic reactant brought into action later. This reversibility of order may point to the transient existence of nonisolable metal complexes (*e.g. (2)*) with two or more organic ligands.

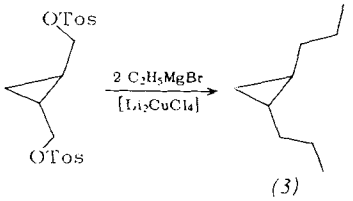


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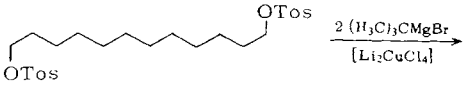
Organic synthesis readily exploits the coordination properties of copper[16]. Important fields of application include aryl-aryl (alkenyl, alkynyl, cyanide) bond formation (Ullmann reaction[17]), oxidative alkenyl-alkenyl bond formation[18-20], the vinylogous addition of Grignard compounds to α,β-unsaturated ketones[21,22], as well as alkyl-alkyl (alkenyl) linkage using lithium organocuprates[23]. The last-mentioned group of CC linkages was considerably simplified when Grignard reagents in the presence of catalytic amounts of a copper salt were found to be equivalent to lithium diorganocuprates[20] (or lithium haloorganocuprates[16] or lithium alkoxyorganocuprates[24]). A subsequent modification—"incubation" of the copper catalyst and reaction with *p*-toluenesulfonates instead of alkyl iodides—has further improved the method and gives excellent yields even in twofold reactions (examples *(3)* and *(4)*; 79% and 99% respectively)[25].

It is suggested that copper(I) becomes part of a mixed association compound *(5)*. A reactive species *(6)* containing formally divalent copper could separate and undergo insertion between carbon and the heteroelement of the electrophilic reactant (alkyl iodide or *p*-toluenesulfonate). The intermediate complex *(7)* then breaks down, with liberation of a hydrocarbon and regeneration of the mixed association compound *(5)*.

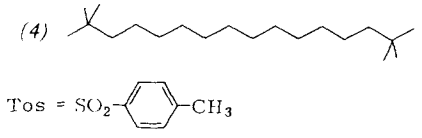
[*] Generally speaking, the 3d orbitals of an Ni^0 complex—occupied by nonbonding electrons—project into the same peripheral outer regions as its $4s4p^3$ hybrid orbitals, which cause the interaction with the ligands. This follows from the greater eccentricity of the d orbitals and is confirmed by their involvement in resonance operations ("back donation"). Ligand loss, which may generate hypovalent complexes—*e.g.* L_2Ni^0—makes the d electrons even more readily accessible.



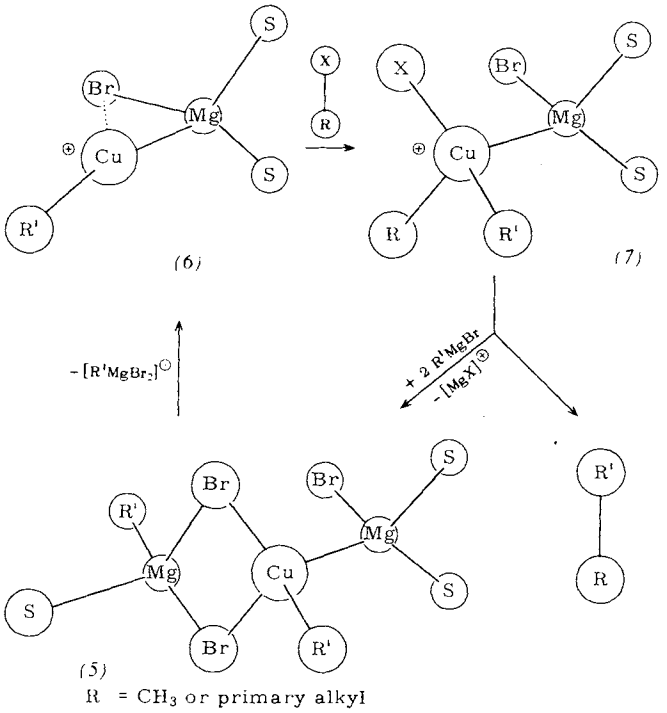
(3)



(4)



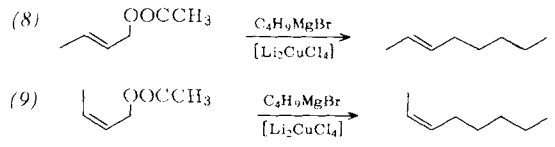
This mechanism[25,26] explains why copper-catalyzed CC bond formation is unsuccessful with *secondary* and especially with *tertiary* halides or *p*-toluenesulfonates RX. Steric hindrance makes the insertion step more difficult or suppresses it entirely. On the other hand, *p*-toluenesulfonates should be superior to alkyl iodides since they envelop the copper atom by chelation and thus facilitate the insertion. In fact, even acetoxy groups, insofar as they are "mobile" when linked



R = CH_3 or primary alkyl
R' = Alkyl, aryl etc.
X = OTos, I
S = Solvent (diethyl ether, tetrahydrofuran)

in the allyl position, undergo the copper-catalyzed displacement reaction, apparently because they also exert a chelating action. The original structure and configuration of the substrate are retained on incorporation into the new olefin formed by reaction of a primary allyl acetate (*e.g. (8)* or *(9)*; 88% and 50% respectively)[25].

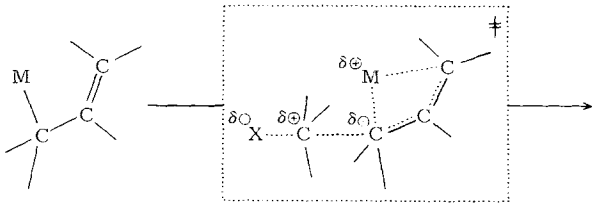
Secondary and tertiary allyl acetates, on the other hand, behave differently—no doubt as a result of greater steric hindrance. Reaction with Grignard reagents in the presence of a copper



catalyst[26] and with lithium diorganocuprates[27,28] results in substitution in the vinylogous position accompanied by a shift of the double bond.

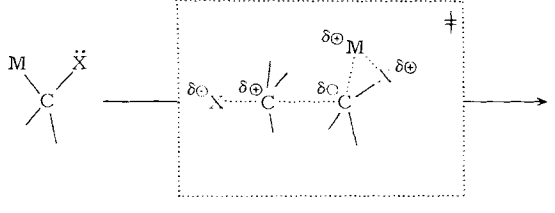
4. Allyl-Alkali Metal Reagents

As long as transition metals were involved the organometallic reactivity was largely shifted towards the metal. The central atom acts as a template to which the reactants are fixed, paves the way for bond formation and eventually awaits a new reaction cycle. Alkali metals and alkaline earth metals may frequently also intervene in the reaction and leave their individual imprint upon the course[3]. However, if they are derivatives of the allyl, propargyl, or benzyl type—in short, if they occupy a resonance-stabilizable position—they often play no more than a passive role. Acting as an auxiliary reaction center the π-bonding system can then involve the metal in the transition state *(10)* and "distract" it, and thereby endow the carbon atom initially carrying the metal with an almost undiminished nucleophilic reactivity.



(10)

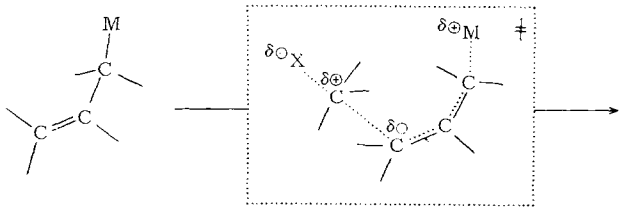
Metalated ethers[29] and thioethers (transition state *(11)*), and especially thioacetals[30-32] as well as ylides (internal carbanion salts!) and amides (free electron pair!) may well owe their unusually high nucleophilicity to this type of exposure of the anionic reaction center.



(11)

For organometallic compounds of the allyl, propargyl, and benzyl type there is of course a second possibility. They can attack the electrophilic reactant with the vinylogous end of the unsaturated system (the γ-position) and continuously replenish the electron density "consumed" from the organometallic bond (transition state *(12)*) during formation of the new CC bond.

It appears reasonable that allylmagnesium and allyllithium compounds should prefer vinylogous attack (S_E2'; *(12)*) to direct substitution (S_E2; *(10)*) since on the one hand small metal atoms hardly "feel" the presence of the π-system as



(12)

long as they are in the proximity of their original position, and on the other hand, direct substitution needs more activation in the initial stages, as cleavage of the CM bond considerably anticipates the formation of a new CC bond (or, in other words, (10) is "less concerted" than (12)). In contrast, allylpotassium compounds should tend rather toward direct substitution on account of their larger and more weakly bound metal atom.

Fortunately, efficient methods exist for the preparation of 2-alken-1-yllithium and -potassium compounds[33, 34], making them readily accessible for systematic investigations.

In the presence of potassium *tert*-butoxide, *n*-butyllithium readily metalates propene at −45 C. Apart from allylpotassium (63 %), the reaction mixture—a pale yellow suspension in hexane—also contains lithium *tert*-butoxide; however, the latter is soluble in benzene or toluene and can thus be removed if desired. The potassium can further be exchanged by a less electropositive metal[34].

Aliphatic, olefinic, or heterofunctionally substituted derivatives of propene (especially substrates of type (13)—(15)) raise new problems: where, and how fast, does hydrogen/metal exchange take place, at which end of the allylic system does the resulting organometallic compound combine with an electrophilic reagent, and what is the configuration of the product?

X–CH=CH–CH$_3$	CH_2=CX–CH_3	CH_2=CH–CH_2X
(13) [(Z) or (E)]	(14)	(15)

4.1. Reactivity

Substituents X subject to p- or d-resonance and able to stabilize carbanions and their organometallic "derivatives" expectedly accelerate hydrogen/metal exchange in the allylic position. Conversely, electron-donating substituents such as alkyl groups, LiO, LiS, and frequently also alkoxy groups, reduce the rate of metalation. Table 1 summarizes these findings.

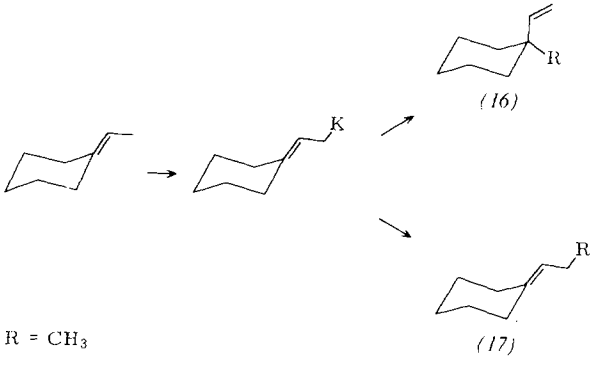
Table 1. Metalation tendency of substrates (13)–(15) according to type of substituent X [a].

X	(13)	(14)	(15)
CH_3 [b]			− −
CH=CH_2 [c]	[d]	[d]	+ +
OR		[e]	±
OLi	[f]	[f]	− −
SR	[e]	[e]	+ +
SLi	[e]	[e]	±

[a] Explanation: Metalation compared to propene:
+ + much faster
+ faster
± unchanged
− slower
− − much slower.
[b] Or another alkyl group.
[c] Or C_6H_5.
[d] Not observable, due to rapid polymerization.
[e] Not yet examined.
[f] The substrates are enolates; experiments are still in progress.

4.2. Regioselectivity

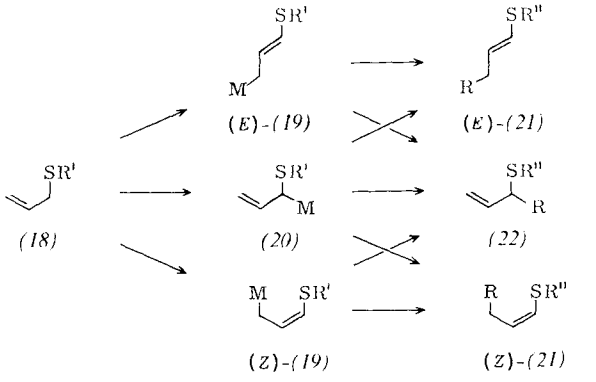
Experience has shown that the preferred bond position selected by the metal is a primary rather than a secondary or, even worse a tertiary carbon atom. Nevertheless, the action of an electrophilic reactant can result in the formation of a more strongly branched product since—as mentioned earlier—attack at the vinylogous position accompanied by a double bond shift proceeds much more readily. While Grignard reagents predominantly or exclusively undergo this vinylog *i. e.* γ-substitution (S_E2'), the behavior of organopotassium compounds is governed by the solvent: in a nonpolar medium (light petroleum) the branched product is formed in considerable amounts (*e. g.* (16); up to 20 %), in tetrahydrofuran or even more basic solvents (tetraglyme, hexamethylphosphoric triamide) the predominant reaction definitely takes place directly at the organometallic bond (S_E2; leading *e. g.*, almost exclusively to (17))[35][*].



(16)

R = CH_3 (17)

It is frequently more difficult to decide which "metalotrope" ("metalomer") predominates in a tautomeric equilibrium. Thus, in the metalation of allylsulfur compounds (18) (*e. g.* allyl phenyl sulfide (18a)) there is only indirect evidence for the assumption that intermediates (20), in which the metal is located on the hetero-substituted carbon, are formed predominantly. (The alternative possibility, a preferred location of the metal at the other end of the allylic system—metalomers (Z)-



(a): R = CH_3; R' = R'' = C_6H_5; M = K
(b): R = $CH_2CH{=}CH_2$; R' = Li; R'' = $CH_2CH{=}CH_2$; M = Li

[*] The fewer bulky alkyl substituents there are hindering access to the vinylogous position, the more effectively γ attack can compete with direct metal exchange (at the α position). In the case of unbranched alkenylpotassium compounds, the two substitution mechanisms are almost equally favored—at least in nonpolar reaction media (cf. Section 4.3). Extending this argument, it is estimated that allylpotassium itself should accept the electrophilic reactant to an overwhelming extent (>85:15) at the metal-free end of the molecule, thereby undergoing a double-bond shift.

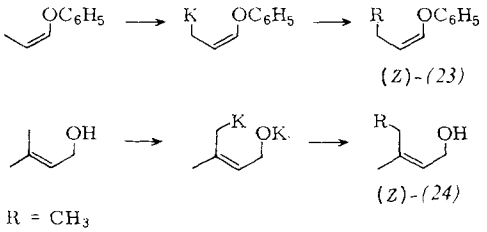
and (*E*)-(*19*)—cannot however be entirely ruled out at this time).

By varying the solvent it is possible to modify the proportions of γ- and α-substituted secondary products (straight-chain or branched derivatives (*21a*) and (*21b*)) within wide limits[36].

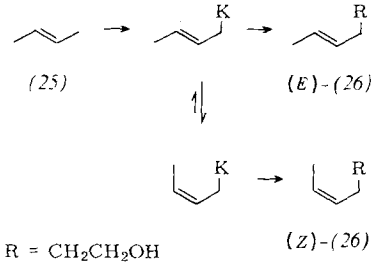
4.3. Stereoselectivity

2-Propene-1-thiolates (*e.g.* (*18*), R′ = Li) can also be metalated with *n*-butyllithium (tetramethylethylenediamine is superior to potassium *tert*-butoxide as the "activator" in this particular case). Although the action of allyl bromide on the organometallic intermediate again yields both γ- and α-substituted products, the thioenol-ether component ((*21b*); 42%) now exists exclusively in the (Z)-configuration[36].

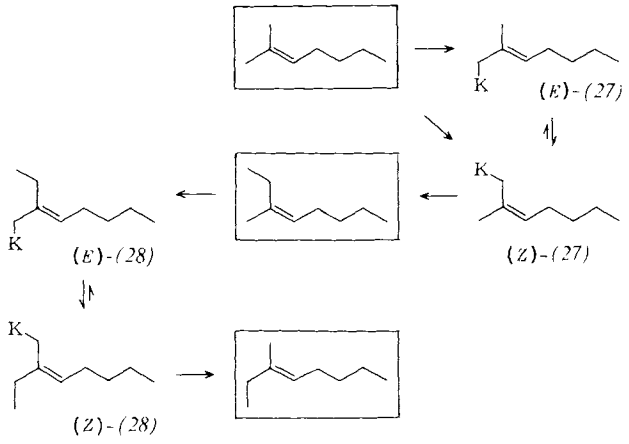
Other substrates also show a marked preference for a particular configuration. Thus, (*Z*)-1-propenyl phenyl ether and 3-methyl-2-buten-1-ol (prenol) are readily converted into isomerically pure homologs (*Z*)-(*23*) (84%) and (*Z*)-(*24*) (7%, accompanied by considerable K_2O elimination to isoprene)[36].



Simple alkenylpotassium compounds lacking any functional groups surprisingly also follow this "*cis*-trend". Whether, and to what extent, this stereochemical peculiarity manifests itself, however, largely depends on the reaction conditions. For short reaction times it is possible to conserve the original configuration of the olefin even after metalation and to "propagate" it. Thus (*E*)-2-butene (*25*) is readily enlarged to (*E*)-4-hexen-1-ol ((*E*)-(*26*); 50%)[37]. Over a period of a few hours, however, the butenylpotassium is almost completely converted from the (*E*)-configuration into its (*Z*) torsional isomer, from which (*Z*)-(*26*) (78%) is readily obtained. A carbon atom carrying a metal thus obviously seeks the proximity of alkyl groups, and these therefore change over to the inner side of the alkenyl system in the course of metalotropy and conformational motion[37].



As a result of this behavior pure (*Z*)-3-methyl-3-octene (45%) may be prepared from 2-methyl-2-heptene and can subsequently be entirely converted into its (*E*)-isomer (60%); hydrogen/metal exchange in the starting material leads to an isomeric mixture of the organometallic compound [(*Z*)- and (*E*)-(*27*)], which exclusively affords the (*Z*)-form after a while. Renewed metalation of the homologous hydrocarbon produced by the action of methyl iodide yields first the alkenylpotassium compound (*E*)-(*28*); this is then isomerized to (*Z*)-(*28*) and liberates (*E*)-3-methyl-3-octene on protolysis[35, 37].



The stereoselectivity attainable by adjusting the equilibrium is approximately 1000:1 in both cases [(*Z*)-(*27*) ⇌ (*E*)-(*27*) and (*Z*)-(*28*) ⇌ (*E*)-(*28*)].

The many cooks who did not spoil the broth are V. David, Dr. G. Fouquet, E. Hammer, Dr. J. Hartmann, Dr. R. Muthukrishnan, and P. Schneider. The ingredients were mainly provided by the Schweizerischer Nationalfonds zur Förderung wissenschaftlicher Forschung, Bern.

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[1] *R. E. Ireland:* Organic Synthesis. Prentice-Hall, Englewood Cliffs, N. J., 1969, p. 3.

[2] Survey: *M. Schlosser*, Angew. Chem. 76, 124, 287 (1964); Angew. Chem. internat. Edit. 3, 287, 362 (1964); cf. also ref. [3].

[3] *M. Schlosser:* Struktur und Reaktivität polarer Organometalle. Springer-Verlag, Heidelberg 1973, pp. 105ff.

[4] *G. Wittig*, Angew. Chem. 66, 10 (1954).

[5] *V. Boekelheide* and *R. A. Hollins*, J. Amer. Chem. Soc. 92, 3512 (1970).

[6] *V. Rautenstrauch*, Chem. Commun. *1970*, 4.

[7] *W. Reppe*, Liebigs Ann. Chem. 582, 1 (1952); *J. Falbe*, Synthesen mit Kohlenmonoxyd. Springer-Verlag, Heidelberg 1967; *G. P. Chiusoli* and *L. Cassar*, Angew. Chem. 79, 177 (1967); Angew. Chem. internat. Edit. 6, 124 (1967); *J. Tsuji*, Accounts Chem. Res. 2, 144 (1969); *G. P. Chiusoli*, Accounts Chem. Res. 6, 422 (1973).

[8] *G. Wittig*, Angew. Chem. 68, 505 (1956); *U. Schöllkopf*, *ibid.* 71, 260 (1959).

[9] *M. Schlosser*, Top. Stereochem. 5, 1 (1970).

[10] *H. Pines*, Synthesis *1974*, 309.

[11] *L. Cassar*, J. Organometal. Chem. 54, C 57 (1973).

[12] Cf. decomposition of thermolabile polyarylmetal compounds: *G. Wittig* and *H. Fritz*, Liebigs Ann. Chem. 577, 39 (1952); *G. Wittig* and *G. Lehmann*, Chem. Ber. 90, 875 (1957); *G. Wittig* and *G. Klar*, Liebigs Ann. Chem. 704, 91 (1967); *G. Wittig* and *K. D. Rümpler*, *ibid.* 751, 1 (1971); *G. Wittig*, *S. Fischer*, and *G. Reiff*, *ibid.* *1973*, 495.

[13] *G. Parker* and *H. Werner*, Helv. Chim. Acta 56, 2819 (1973).

[14] *K. Tamao*, *M. Zembayashi*, *Y. Kiso*, and *M. Kumada*, J. Organometal. Chem. 55, C 91 (1973).

[15] *M. F. Semmelhack* and *L. Ryono*, Tetrahedron Lett. *1973*, 2967.

[16] *J. F. Normant*, Synthesis *1972*, 63.

[17] *P. E. Fanta*, Chem. Rev. 64, 613 (1964).

[18] *G. M. Whitesides* and *C. P. Casey*, J. Amer. Chem. Soc. 88, 4541 (1966); cf. also *G. M. Whitesides*, *J. SanFilippo*, *C. P. Casey*, and *E. J. Panek*, *ibid.* 89, 5302 (1967).

[19] *T. Kauffmann* and *W. Salm*, Angew. Chem. 79, 101 (1967); Angew. Chem. internat. Edit. 6, 85 (1967).

[20] *M. Tamura* and *J. Kochi*, Synthesis *1971*, 303.
[21] *M. S. Kharasch* and *P. O. Tawney*, J. Amer. Chem. Soc. *63*, 2308 (1941).
[22] *H. O. House*, *W. L. Respess*, and *G. M. Whitesides*, J. Org. Chem. *31*, 3128 (1966).
[23] *G. H. Posner*, Org. React. *19*, 1 (1972).
[24] *G. H. Posner* and *C. E. Whitten*, Tetrahedron Lett. *1973*, 1815.
[25] *G. Fouquet* and *M. Schlosser*, Angew. Chem. *86*, 50 (1974); Angew. Chem. internat. Edit. *13*, 82 (1974).
[26] *M. Schlosser*, *E. Hammer*, and *G. Fouquet*, unpublished.
[27] *P. Rona*, *L. Tökes*, *J. Tremble*, and *P. Crabbé*, Chem. Commun. *1969*, 43.
[28] *R. J. Anderson*, *C. A. Henrick*, and *J. B. Siddall*, J. Amer. Chem. Soc. *92*, 735 (1970).
[29] *M. Schlosser*, *B. Schaub*, *B. Spahić*, and *G. Sleiter*, Helv. Chim. Acta *56*, 2166 (1973).
[30] *A. Fröling* and *J. F. Arens*, Rec. Trav. Chim. Pays-Bas *81*, 1009 (1962).
[31] *W. E. Truce* and *F. E. Roberts*, J. Org. Chem. *28*, 961 (1963).
[32] *D. Seebach*, Synthesis *1969*, 17.
[33] *M. Schlosser*, J. Organometal. Chem. *8*, 9 (1967).
[34] *M. Schlosser* and *J. Hartmann*, Angew. Chem. *85*, 544 (1973); Angew. Chem. internat. Edit. *12*, 439 (1973).
[35] *M. Schlosser*, *P. Schneider*, and *J. Hartmann*, unpublished.
[36] *J. Hartmann*, *R. Muthukrishnan*, and *M. Schlosser*, Helv. Chim. Acta, in press.
[37] *M. Schlosser*, *J. Hartmann*, and *V. David*, Helv. Chim. Acta, *57*, 1567 (1974).

Biochemistry of the Peroxisome in the Liver Cell

By Helmut Sies[*]

The marker enzyme of the peroxisome—a phylogenetically old yet only recently discovered cell organelle—is catalase, a hemoprotein which decomposes hydrogen peroxide catalatically as well as peroxidatically. In the peroxisomes, catalase is associated with H_2O_2-producing oxidases and other enzymes. Also in parenchymal cells such as liver and kidney cells part of the reduction of oxygen occurs *via* formation of H_2O_2. A central role in peroxisomal H_2O_2-metabolism is played by the active intermediate, catalase-Fe^{3+}-H_2O_2 (Compound I), which is distinguished from free catalase by specific absorption bands. Organ photometry on intact hemoglobin-free perfused rat liver in order to measure Compound I selectively provides a direct insight into the dynamics of the H_2O_2 metabolism which takes place in the range of nanomolar concentrations. Endogenously, 1 g of liver forms approximately 50 nmol of H_2O_2 per min. The turnover number, which in the steady state is $<10\,min^{-1}$ in the cell as compared to $>10^8\,min^{-1}$ for the isolated enzyme with an excess of substrate, can be increased to approximately $10^2\,min^{-1}$ by intracellular stimulation of the H_2O_2 production (*e.g.* by glycolate or urate). The peroxidatic oxidation of hydrogen donors (*e.g.* methanol and ethanol), favored relative to the catalase pathway at low turnover numbers, is of importance in normal metabolism and in pathological conditions.

1. Introduction

As follows from Table 1, the subject of this report has a history going back approximately 150 years.

Research on the biological and chemical aspects of catalase and of hydrogen peroxide metabolism strongly revived in recent years. It received an essential impetus from cell biology. In 1954 *Rhodin* observed electron-optically cytoplasmic inclusions, "microbodies"[1], in the renal tubule cells of the mouse, which also occur in the liver cells[2] and in many other cell types of aerobic organisms. Little was known about the biochemical function of these cell organelles; in the beginning they were regarded as precursors of the mitochondria or as forms of lysosomes. As revealed in studies on homogenates and cell fractions, some oxidases as well as catalase are "particulate"[3-6]; however, they could not be related to the mitochondria, microsomes, or lysosomes. From the behavior of these enzyme activities during the isopyknic density-gradient centrifugation of cell fractions, and from morphological studies, *de Duve* and his co-workers concluded that these were associated with the "microbodies"[7-12]. The presence of H_2O_2-producing oxidases together with H_2O_2-decomposing catalase led to the concept of these cell organelles acting as a functional unit in H_2O_2 metabolism, "peroxisomes"[11,12].

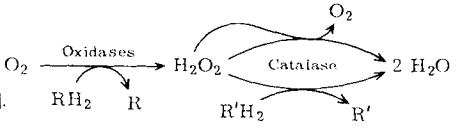
While at the beginning of this century interest in research on the nature of cell respiration was focused on the hemoprotein catalase, it became almost forgotten after the discovery of the "Atmungsferment" cytochrome oxidase. Only in the last few years has it become clear that catalase plays an important part in its domain of biological oxidation, the key position being occupied by the active intermediate catalase-Fe^{3+}-H_2O_2 (Compound I), discovered by *Chance* in 1947[13] (Scheme 1a and 1b).

The function of the peroxisome in intracellular peroxidatic and catalatic reactions can only be partially understood in studies with isolated peroxisomes; rather, the system must be investigated in intact cells or organs. Spectrophotometry of intact organs, developed in recent years, affords a direct

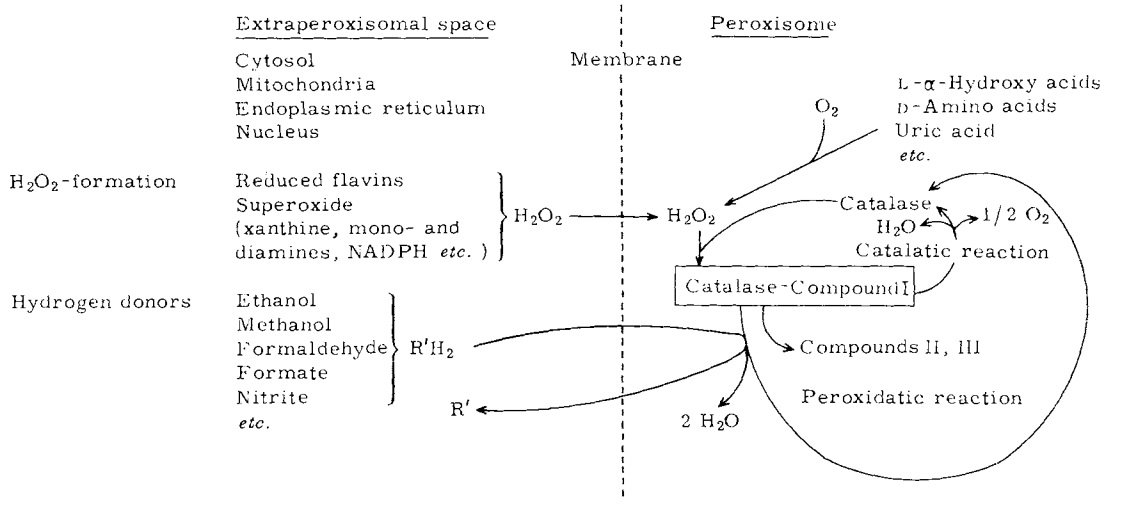
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Table 1. Development of knowledge about H_2O_2, catalase, and peroxisomes.

Discovery	Year	Author	Ref.
H_2O_2 and its decomposition by tissue	1818	*Thénard*	[66]
Establishment of the name "catalase"	1901	*Loew*	[67]
Iron in the active group of catalase	1923	*Warburg*	[70]
Peroxidatic reaction of catalase	1936, 1945	*Keilin* and *Hartree*	[77, 78]
Crystallization of catalase	1937	*Sumner* and *Dounce*	[74a]
Crystallization of peroxidase	1942	*Theorell*	[74b]
Active intermediate (catalase-Fe^{3+}-H_2O_2 = Compound I)	1947	*Chance*	[13]
Compound I in bacteria	1952	*Chance*	[131]
"Microbodies"	1954	*Rhodin*	[1]
Glutathione peroxidase	1957	*Mills*	[143]
Peroxisome as a functional unit of H_2O_2 metabolism	1966	*deDuve* and *Baudhuin*	[12]
Inducibility of peroxisomes	1966	*Svoboda* and *Azarnoff*	[47]
Superoxide dismutase	1969	*McCord* and *Fridovich*	[124a]
Compound I in intact perfused rat liver	1970	*Sies* and *Chance*	[116]
Compound I in liver of anesthetized rat	1974	*Chance, Oshino, Sugano,* and *Jamieson*	[151]



Scheme 1a. *deDuve*'s scheme [12].



Scheme 1b. The role of oxidases and catalase and of catalase Compound I in peroxisomal H_2O_2 metabolism.

insight into cellular metabolism. The possibilities that organ photometry offers for research on the dynamics of intracellular compartmented processes can be demonstrated by the example of catalase Compound I in isolated perfused rat liver.

In spite of the efforts of many research groups, the manifold functions of the peroxisomes in animal cells are at present incompletely understood (cf. reviews on the cell biology of peroxisomes[12, 14–17], and on the enzymology of catalase[18–20]).

2. The Peroxisome

The peroxisome consists of a matrix surrounded by a unit membrane, and it contains a central core region called the crystalloid (Fig. 1).

Rat liver cells contain approximately 350—400 of these organelles. Table 2 gives a list of enzymes in rat liver peroxisomes, from which it follows that only about half of the peroxisomal protein is accounted for by the known enzyme activities. The nature of the remaining proteins is still unknown. Peroxisomes can be separated from other cell organelles by isopyknic density gradient centrifugation. In Figure 2 this is demonstrated by the localization of the activities of the marker enzymes of the peroxisomes, the mitochondria, microsomes, and lysosomes in the density gradient.

Table 2. Enzyme activities [a] found in rat liver peroxisomes (after [24–28]).

EC number	Enzyme (trivial name)	Fraction of peroxisomal protein [25] [%]
1.1.1.8	Glycerol-3-phosphate dehydrogenase	n. d. [b]
1.1.1.26	Glyoxylate reductase [NAD]	n. d.
1.1.1.29	Glycerate dehydrogenase [NAD]	n. d.
1.1.1.42	Isocitrate dehydrogenase [NADP]	≤25
1.1.1.–	Glyoxylate reductase [NADP]	n. d.
1.1.1.–	Glycerate dehydrogenase [NADP]	n. d.
1.1.3.1	Glycolate oxidase	n. d.
1.1.3.α	L-α-Hydroxy acid oxidase	≤ 3
1.4.3.3	D-Amino acid oxidase	≤ 2
1.7.3.3	Urate oxidase	≤10
1.11.1.6	Catalase	≤16
2.3.1.7	Carnitine acetyltransferase	n. d.

[a] Some of the homologous activities listed may be ascribed to the same enzyme.
[b] n. d. = not determined.

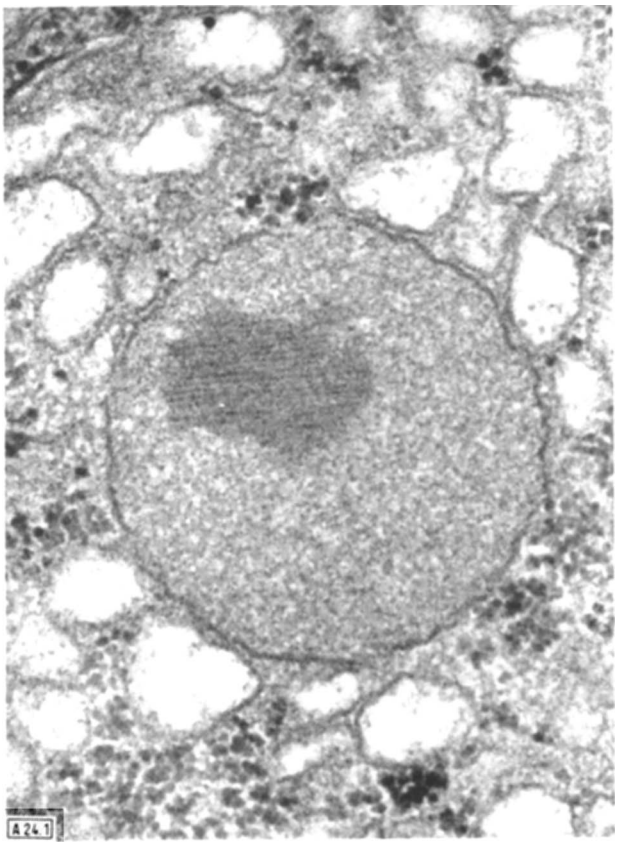


Fig. 1. Peroxisome from rat liver. The central region shows the urate oxidase present in the form of tubuli [21]. Magnification 82000 ×. The electron micrograph was obtained by courtesy of Prof. *F. Miller*.

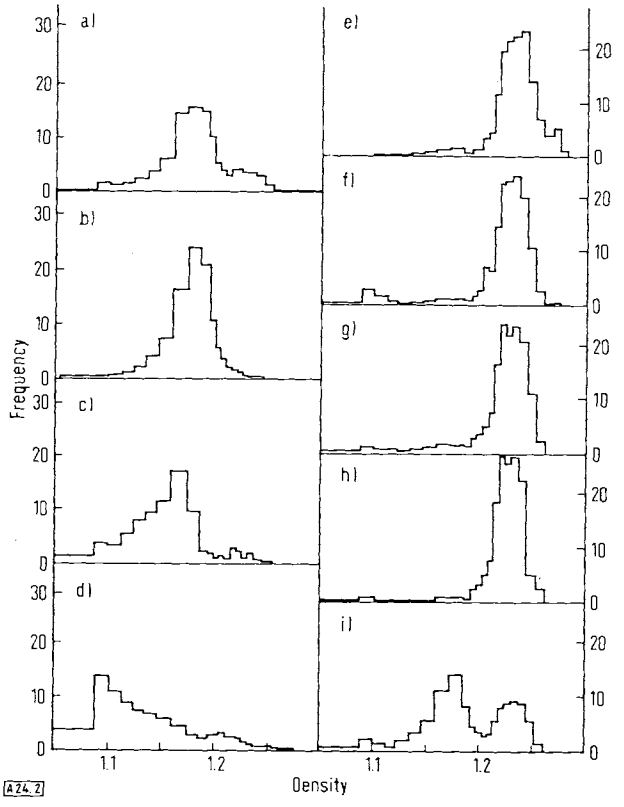


Fig. 2. Equilibrium density distribution of marker enzyme activities in a λ-fraction [10] from rat liver in a sucrose gradient. a) Total protein; below: marker enzymes for b) mitochondria (cytochrome oxidase), c) microsomes (glucose-6-phosphatase), and d) lysosomes (acid phosphatase); right: peroxisome enzymes: e) urate oxidase, f) catalase, g) D-amino acid oxidase, h) L-α-hydroxy acid oxidase, i) isocitrate dehydrogenase (at the density of 1.23 to 1.24). The $NADP^+$-dependent isocitrate dehydrogenase has a bimodal distribution. After treatment of the rat with Triton W-1339 [22] the lysosomes have a particularly low density (from [23]).

With respect to the functional morphology of the peroxisome, it may be mentioned that the organelle is freely permeable to low-molecular-weight solutes (zero osmotic space). Little

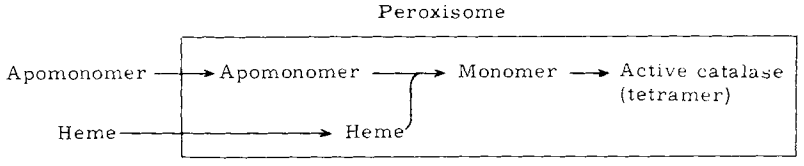
Table 3. Cell biology and cell chemistry of rat liver organelles with oxygen-activating systems.

Parameter	Peroxisomes	Mitochondria	Microsomes	Ref.
Volume fraction in the liver [%]	1.16	18.1	12.8	[30]
Number [ml^{-1}]	62×10^9	280×10^9	—	[30]
Equilibrium density in sucrose gradient [g/ml]	1.23	1.18		
Sucrose space [ml/g dry liver]	2.5	0.9	—	[31]
Osmotic space [ml/g dry liver]	0	0.6	—	[31]
Membrane	"Unit membrane"	Inner and outer membrane (one "unit membrane" each)	"Unit membrane", rough and smooth reticulum	
Phospholipid content [mg/mg protein]	0.09	0.20	0.32	[29]
Cardiolipin	−	+	−	
DNA	−	+	−	
Protein synthesis system	−	+	+	
"Terminal-oxidase"	Catalase	Cytochrome oxidase	Cytochrome P-450 "cytochrome b_5 oxidases"	
Inducibility of components	Hypolipidemic substances [a] salicylates	Thyroxine	Barbiturates, alicyclic hydrocarbons	
Marker enzyme	Catalase	Cytochrome oxidase, succinate dehydrogenase	Glucose 6-phosphatase, cytochrome P-450	
Half-life	1.5—2 d	Proteins of the inner membrane 12—13 d, those of the outer membrane 4 d	Proteins in rough and smooth reticulum 4 d	[32—36]

[a] Example: Clofibrate (ethyl 2-(*p*-chlorophenoxy)isobutyrate).

is known about specific permeability properties of the peroxisomal membrane, which resembles the microsomal membrane in its phospholipid composition[29]. Some properties of peroxisomes are compared in Table 3 with the properties of two other cell organelles with oxygen-activating systems, the mitochondria and the endoplasmic reticulum (microsomes).

mental evidence[56] (cf. also [57,58]). The apomonomer, with a half-life of 14 min is brought into the peroxisome as such in a still unknown manner and there receives the heme group. The apomonomer and the monomer amount respectively to 1.6% and 0.5% of the total amount of catalase; their half-life is less than 1 h (Scheme 2).



Scheme 2. Biosynthesis of catalase (according to [56]).

2.1. Cytochemistry of Peroxisomal Catalase

Cytochemically, catalase is regarded as the marker enzyme of peroxisomes[37], on the basis of the 3,3',4,4'-biphenyltetramine (diaminobenzidine) oxidase activity of catalase[38-41]. This peroxidatic activity of catalase is only observed after fixation of the enzyme, *e. g.* with glutaraldehyde. This applies both to catalase within the peroxisome in the cell[42] and to the isolated enzyme[43], and probably depends on a conformational change of the protein. This is also supported by the increase in reactivity for peroxidatic substrates if the enzyme has been subjected to trypsin degradation under mild conditions or to denaturation by alkali[44].

The question whether an appreciable amount of catalase exists extraperoxisomally *in vivo*[45] and whether this is demonstrable cytochemically[41], cannot yet be answered due to methodological reasons.

2.2. Turnover and Biogenesis of the Peroxisome

The organelle is subject to relatively rapid turnover *in toto*; its measured half-life is approximately 1.5—2 days[32,33].

The stationary content of peroxisomes in the liver cell depends on numerous hormonal, nutritional, and pharmacological influences (cf.[15,46]). For example, ethyl 2-(*p*-chlorophenoxy)-isobutyrate (Clofibrate) causes an increase in the number of peroxisomes[47], which increases the proportion of peroxisomes in the total volume of the liver cell from about 2% to about 17%[48]. This increase is related to an increase in the content of antigen reacting with anticatalase serum[49], *i. e.* the amount of catalase is also increased. The activity of the peroxisomal oxidases given in Table 2 remains unchanged[50], while the activity of the glycerol-3-phosphate dehydrogenase also increases[51]. Similar effects are observed *e. g.* with acetylsalicylic acid[52]. The increase in the number of peroxisomes by Clofibrate does not depend on catalase synthesis, since it also occurs when the formation of catalase is inhibited by allylisopropylacetamide[53].

The biogenesis of the organelle is still in dispute. Close morphological and biochemical relationships to the endoplasmic reticulum have been described repeatedly[54,55]. Investigations on catalase biosynthesis are of special importance in this context. The hypothesis that catalase is first formed essentially within the peroxisomes from extraperoxisomally synthesized precursors has been supported by experi-

Histochemical attempts to establish the passage of active catalase through the free cytoplasm prior to incorporation into the peroxisome[41] led to equivocal results owing to methodological problems[59,60]. In addition, the question whether catalase protein is synthesized *in vivo* on free and/or membrane-bound polysomes, has not been answered unambiguously[61-64]. *Redman et al.*[64] did not find catalase in the rough endoplasmic reticulum. Export proteins such as albumin and intracellular proteins such as catalase could therefore be synthesized at separate sites. *In vitro*, however, membrane-bound as well as free ribosomes can incorporate ^{14}C-leucine into enzymatically active catalase[62,65].

3. Enzymology of Catalase

Catalase is a tetrameric enzyme with four probably identical subunits and four heme groups; the iron in the heme is trivalent. In contrast to hemoglobin, there are no indications of cooperativity between the subunits. Its molecular weight is about 240000 dalton. The methods of its isolation and crystallization, as well as its structural properties and the amino-acid composition, have been reviewed by *Deisseroth* and *Dounce*[20]. The catalatic action of catalase [equations (1a) and (1b), cf. Section 3.1] was one of the first enzymatic functions discovered. At the discovery of hydrogen peroxide in 1818 *Thénard* already observed that this substance is decomposed in the presence of animal tissues with evolution of oxygen[66], a reaction which also occurs on platinum surfaces. Catalase was at the center of intensive discussions concerning the nature of enzyme action[68,69], in particular the heavy metal catalysis in enzymes[70-73], and after its crystallization[74] served as the object of numerous studies[18-20,75,76] on the biocatalysis by hemoproteins.

3.1. Catalase Complexes

Using rapid mixing methods, *Chance*[13] discovered spectrophotometrically an active intermediate, "Compound I", in the reaction of catalase with H_2O_2. Compound I is characterized by a decreased absorbance at 405 nm and an increased absorbance at 665 nm (Fig. 3). On the addition of alcohols to Compound I the absorbance again increases rapidly, *i. e.* free catalase is regenerated through the peroxidatic reaction discovered by *Keilin* and *Hartree*[77,78] (eqs. (1a) and (1c)):

$$\text{Catalase-Fe}^{3+} + H_2O_2 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{Catalase-Fe}^{3+}\text{-}H_2O_2 \quad (1a)$$
(free catalase; e) (x) (Compound I; p)

$$\text{Catalase-Fe}^{3+}\text{-}H_2O_2 + H_2O_2 \xrightarrow{k_4'} \text{Catalase-Fe}^{3+} + 2H_2O + O_2 \quad (1b)$$

$$\text{Catalase-Fe}^{3+}\text{-}H_2O_2 + C_2H_5OH \xrightarrow{k_4} \text{Catalase-Fe}^{3+} + 2H_2O + CH_3CHO \quad (1c)$$
(hydrogen donor; a)

e, x, p, a, see Section 3.2.

The notation "catalase-Fe^{3+}-H_2O_2" for Compound I should indicate that the heme is occupied by H_2O_2 ("heme occupancy"). It is noteworthy that one mole of catalase does not simultaneously bind four moles of H_2O_2—*i.e.* one molecule per heme—but only approximately 1 to 1.6 moles of H_2O_2[79]. The other heme groups remain free. However, if an alkyl hydroperoxide, *e. g.* methyl or ethyl hydroperoxide, is used instead of H_2O_2, all four catalase subunits can be transformed into Compound I ([80], cf. [81]).

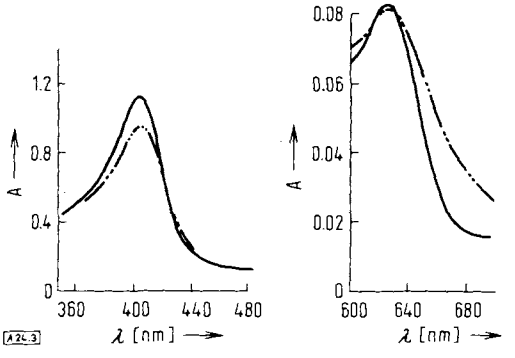


Fig. 3. Absorption spectra of purified catalase (----) from rat liver (catalase heme 9.3 μmol/l). Compound I (–·–·–) was obtained with H_2O_2 (23.5 μmol^{-1} min^{-1}) from the glucose oxidase reaction (after [82]).

The chemical structure of Compound I is still unknown[20]. Recent experiments with peracids indicate a reaction of the type:

$$\text{Enzyme} + H_2O_2 \rightarrow \text{Enzyme} = O + H_2O$$

which is probably followed by peroxidase[83–86].

The other catalase complexes (Compound II and Compound III) are catalatically inactive. Compound II has a low peroxidatic activity with respect to phenols. Indications of the occurrence of these compounds in normal intact liver are lacking[87], and therefore the compounds will not be discussed further here. Compound II is formed by the reduction of Compound I with H_2O_2, with phenols, or with ascorbate[88]. The relationships between Compounds I, II, and III and the donors have been reviewed by *Nicholls* and *Schonbaum*[18].

In the catalase-HCN complex[89, 90], which has a dissociation constant of 10^{-6} to 10^{-5} mol/l, each of the four heme groups carries one HCN molecule. The complex is characterized spectrophotometrically, *e. g.* by a minimum of 624 nm as compared to free catalase.

In the reaction between azide and Compound I the iron is reduced and catalase-Fe^{2+}-NO is formed[91–93].

A covalent complex is produced in an irreversible reaction between 3-amino-1,2,4-triazole[94, 95] and catalase in which a histidine group is involved[96]. The heme is then no longer[97] or almost not[98] capable of binding peroxides or ligands such as HCN.

3.2. Steady State Kinetics of Catalase

The kinetic constants k_1, k_4, and k_4' of eqs. (1a)—(1c) were determined for the isolated enzyme (Table 4). For the kinetic analysis of the steady state of the catalase system it has been found, using *Chance*'s nomenclature[79, 103]:

Table 4. Kinetic constants of catalase [see eqs. (1a)—(1c)]. Some of the values were not measured directly but were calculated from indirect measurements. They indicate the order of magnitude of the values at 20—22 °C. More recent calculations [102] lead to slightly lower values of k_1 and k_4'.

Constant		Preparation	Ref.
k_1	1.7×10^7 l mol^{-1} s^{-1}	Rat liver	[79]
k_4'	2.6×10^7 l mol^{-1} s^{-1}	Rat liver	[79, 99] [a]
k_4	$(0.2—1.0) \times 10^3$ l mol^{-1} s^{-1}	Horse erythrocytes	[13, 79, 100] [b]
k_2	$(0—7.5) \times 10^{-3}$ s^{-1}	*M. lysodeikticus*	[101, 86]

[a] Calcd. by eq. (5a) with $p_M/e = 0.4$.
[b] For ethanol and methanol.

$$\frac{dp}{dt} = k_1 x(e-p) - k_4' x p - (k_2 + k_4 a)p \quad (2)$$

$$\frac{dx}{dt} = \frac{dx_n}{dt} - k_1 x(e-p) - k_4' x p + k_2 p \quad (3)$$

$$\frac{da}{dt} = -k_4 a p \quad (4)$$

e = concentration of the total catalase heme
p = concentration of Compound I
x = H_2O_2 concentration
dx_n/dt = steady state rate of H_2O_2 formation
a = hydrogen donor concentration.

In the case of a steady state of Compound I ($dp/dt = 0$) and the rate of H_2O_2 formation (dx_n/dt = const.), and for the condition $k_2 = 0$, the result for the fraction of the total catalase heme e existing as Compound I (p) (*i.e.* for the heme occupancy) is:

$$\frac{p_m}{e} = \left(1 + \frac{k_4'}{k_1} + \frac{k_4 a_0}{k_1 x_m}\right)^{-1} \quad (5)$$

where the subscript m denotes the steady state. As $x_m \rightarrow \infty$, or $a_0 = 0$ and $x_m \neq 0$, $p_m \rightarrow p_M$; thus

$$\frac{p_M}{e} = \left(1 + \frac{k_4'}{k_1}\right)^{-1} \quad (5a)$$

Equation (5a) demonstrates a simple relationship between the maximal heme occupancy p_M/e existing at the maximal rate of H_2O_2 formation and the second-order rate constants for the formation and catalatic degradation of Compound I.

Another useful relationship describes the catalase reaction for the condition that the hydrogen donor concentration a

is chosen so that $p_m = p_M/2$. In the steady state the donor concentration for half-maximal heme occupancy is directly proportional to the steady state rate of H_2O_2 formation dx_n/dt and inversely proportional to the total heme concentration e[103]:

$$a_{p_m = p_M/2} = \left(\frac{\left(3\frac{k'_4}{k_1} + 1\right)k_4}{2\left(\frac{k'_4}{k_1} + 1\right)} \right)^2 \times \frac{1}{e}\frac{dx_n}{dt} \qquad (6)$$

$\frac{1}{e}\frac{dx_n}{dt}$ = steady state turnover number

From eq. (6) it follows that the catalase system does not have a "Michaelis constant" for H_2O_2 or for the hydrogen donor a. Rather, the ratio of the H_2O_2-formation rate and the concentration of the catalase heme (steady state turnover number) plays a role in the steady state concentration of compound I and hence in the donor concentration required for half-maximal decomposition of Complex I. As will be shown below, these relationships are important for the evaluation of the catalatic and peroxidatic reactions in biological systems.

In order to illustrate this point, two examples of experiments with isolated rat liver catalase are given. Figure 4 shows how the steady state heme occupancy p_m/e depends on the steady state turnover number. Both the H_2O_2 formation rate

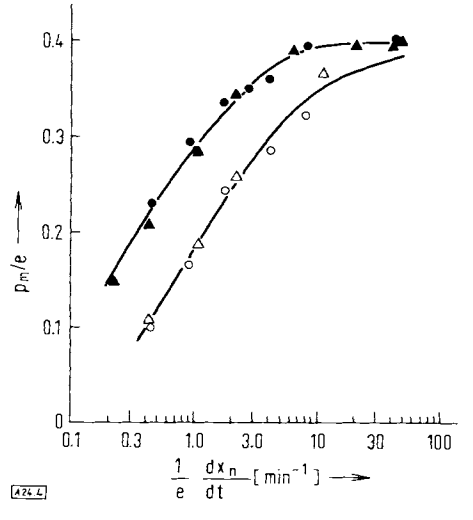


Fig. 4. Dependence of steady state heme occupancy of catalase (p_m/e) on the steady state turnover number (H_2O_2 formation rate/catalase heme concentration), measured with isolated rat liver catalase. The H_2O_2-formation rate (●, ○) was varied from 0.3 to 100 μmol l^{-1} min^{-1} and the catalase heme concentration (▲, △) from 0.1 to 12 μmol/l. Stimulation of the peroxidatic pathway by addition of ethanol (0.1 mmol/l) lowers the steady state heme occupancy (right-hand curve, open symbols). After [82].

(by varying the glucose plus glucose oxidase system) and the catalase heme concentration are varied. As expected, the curve shifts to the right when the peroxidatic pathway competes (by the addition of ethanol).

Figure 5 demonstrates how the partition into peroxidatic and catalatic reactions depends on the rate of H_2O_2 formation and on the concentration of hydrogen donor, in this case ethanol. An exclusively peroxidatic reaction can only be achieved at extremely high donor concentrations and at low turnover numbers[104, 105].

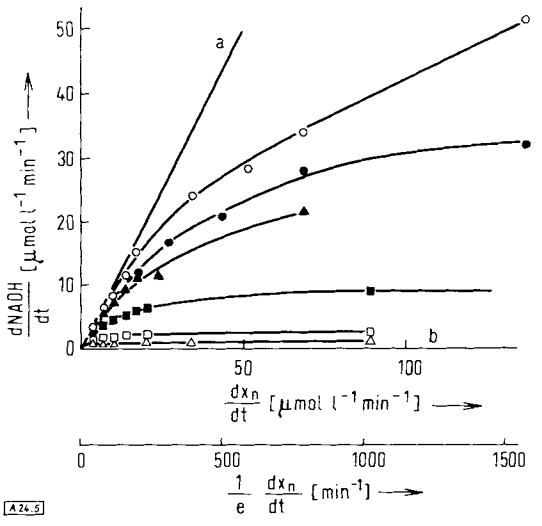


Fig. 5. Distribution of H_2O_2 decomposition between "peroxidatic" and "catalatic" pathways; a, 100% "peroxidatic"; b, 100% "catalatic" reaction. The oxidation rate of ethanol (given as the rate of formation of NADH) is illustrated graphically at several steady state H_2O_2 formation rates dx_n/dt for the following ethanol concentrations: ○, 100; ●, 50; ▲, 25; ■, 5; □, 1; △, 0.33 mmol/l (after [105]).

4. State of Catalase in Hemoglobin-Free Perfused Rat Liver

4.1. Organ Photometry of Catalase Compound I

Since it can be assumed that the H_2O_2 present in peroxisomes is indicated in the form of Compound I, the photometry of this complex allows a direct insight into the metabolism of H_2O_2 and its reaction partners. If the rat liver is perfused with a perfusion fluid free from hemoglobin, optical methods can be used without major difficulty[106–108]; the metabolism of the catalase-containing erythrocytes does not interfere. *Brauser*[109] used the light passing through the lobe of the perfused liver for absorbance measurements (photometry in transmitted light as opposed to reflection photometry), a method that was also used successfully on isolated tissues such as muscle preparations[110–112]. Changes in the steady state content of catalase Compound I in the liver can be detected in the blue (*e.g.* at 405 nm) and in the red spectral regions (*e.g.* at 660 nm).

The problem in the photometry of an organ, a multi-component system, of assigning the measured signals to transitions of specific components, is largely solved by the use of the dual wavelength technique[109–113] and of difference absorption spectra[114, 115]. Since other hemoproteins hardly interfere at the absorbance peak in the red region, the absorbance difference 660—640 nm proves to be best suited with the perfused liver for specific detection of the transition between catalase Compound I and catalase[116, 117].

As Figure 6 shows, the absorbance difference increases upon withdrawal of oxygen (causing an interruption of H_2O_2 formation) and upon the addition of an excess of methanol (causing peroxidatic degradation of Compound I). The two effects are not additive. They are two independent metabolic transitions in which catalase is regenerated from Compound I. The figure shows further that the absorbance difference decreases upon infusion of glycolate. This reflects the increase in intracellular

H_2O_2 production by the flavin enzyme, glycolate oxidase. When catalase is irreversibly inhibited by 3-amino-1,2,4-triazole, both the methanol effect and the effect of withdrawal of oxygen are almost completely lacking[116].

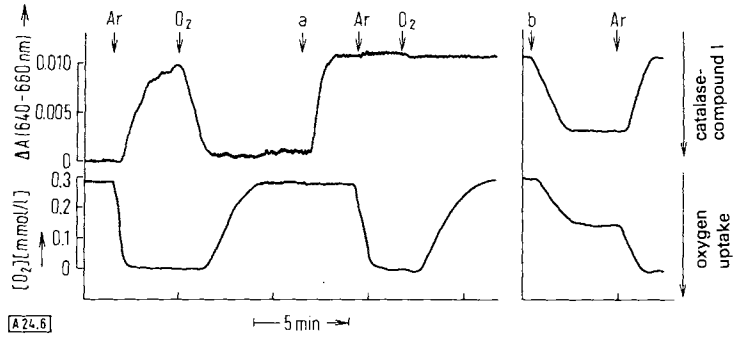


Fig. 6. Upper trace: Left: Recording of the absorbance difference ΔA (640–660 nm) of a perfused liver lobe. The decrease in the catalase Compound I by withdrawal of oxygen or by infusion of methanol (2.5 mmol/l at a) results in a rise of ΔA. Right: Re-formation of Compound I due to H_2O_2 formation from infused sodium glycolate (2mmol/l at b in the presence of 1mmol/l of methanol).
Lower trace: Oxygen concentration in effluent perfusate (after [116]).

4.2. Heme Occupancy of Catalase

Since a continuous endogenous H_2O_2 production in the liver (Figure 6) has been demonstrated, a system of measurement can be devised on the basis of the relationships obtained from the isolated enzyme, which provides information on the state of the enzyme in the intact organ. The heme occupancy $p_m/e=0$ is obtained by an excess of methanol, the maximal heme occupancy $p_m/e=p_M/e$ by an excess of glycolate, and under the same conditions in the perfused organ the catalase-HCN complex is used as a measure of the total catalase heme.

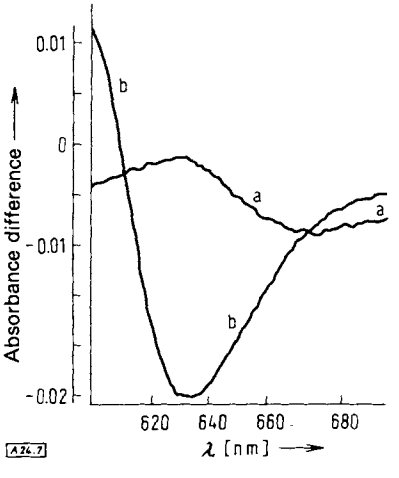


Fig. 7. Absorbance difference spectra of hemoglobin-free perfused rat liver. a) Catalase Compound I, b) HCN-catalase (as a measure of catalase heme). The reference spectrum is that of free catalase in the liver. The spectra correspond to metabolic steady states (see text); they were recorded with a Rapidspektroskop [118]. An instrument computer was used for signal averaging and subsequent digital subtraction according to the method of *Brauser et al.* [114] (after [82]).

Figure 7 shows two absorbance difference spectra. Sodium glycolate (2 mmol/l), methanol (4.8 mmol/l), and methanol (4.8 mmol/l) *plus* sodium cyanide (0.05 mmol/l) were successively infused into the perfusate entering the liver, for 2 to 3 min each. During each of the steady states corresponding to these three conditions 256 absorption spectra of a lobe of the liver were taken within 12 s in the range 600—700 nm and stored. Spectrum a corresponds to the absorbance difference of the liver, obtained by digital subtraction, between the state in the presence of methanol and that in the presence of glycolate, *i.e.* it shows the decrease of the maximal heme occupancy of catalase Compound I to zero heme occupancy. Spectrum b corresponds to the absorbance difference of the liver between the state in the presence of methanol plus cyanide and that in the presence of methanol, *i.e.* it shows the formation of HCN-catalase from free catalase (in the range around 610 nm there is a small contribution by cytochrome oxidase).

With the aid of the difference extinction coefficients[82] determined for catalase isolated from rat liver, a maximal heme occupancy $p_M/e=0.38$ can be calculated from ΔA (640—660 nm) of spectra a and b. Hence the maximal heme occupancy of rat liver catalase *in vitro* (Fig. 4) and *in situ* (Fig. 7) are similar. According to eq. (5a), this means that the catalase molecule has a comparable rate constant ratio k'_4/k_1 at the dilution employed *in vitro* (approximately 10^{-6} mol/l with respect to heme) and with the concentration occurring within the peroxisome *in situ* (approximately 10^{-3} mol/l with respect to heme, see below).

The endogenous steady state of the heme occupancy can be measured by determining the extreme states with methanol and glycolate. In Figure 8 it is 3/4 of the maximal value.

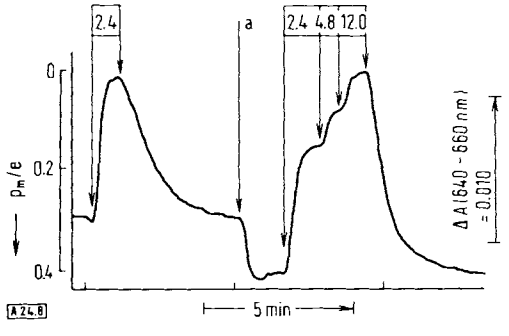


Fig. 8. Recording of the absorbance difference ΔA (640—660 nm) of a perfused liver lobe. Higher methanol concentrations are necessary (see eq. (6) and Fig. 4) for decomposition of Compound I during the stimulation of H_2O_2 formation by glycolate (addition of 2 mmol/l at a). The endogenous heme occupancy is 3/4 of the maximum value. The relevant methanol concentrations (in mmol/l) are given in the upper panel (after [82]).

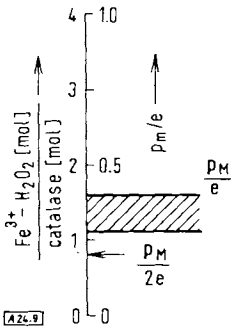


Fig. 9. Schematic representation of the heme occupancy p_m/e of catalase. The shaded region corresponds to the heme occupancy observed in the liver in the endogenous steady state. The maximum value p_M/e is produced by glycolate, urate, *etc.*, and the heme occupancy of zero by withdrawal of oxygen, or by methanol, ethanol, *etc.*

In addition, it can be seen that with increasing the rate of H_2O_2 formation the methanol concentration required for the decomposition of Compound I increases (cf. eq. (6)). The findings and definitions are summarized in Figure 9.

4.3. Catalase Content

Enzyme contents per gram of organ are usually determined from the activity measured in the homogenate and from the specific activity of the isolated enzyme, or by quantitative immunological methods. In another method, which does not require destruction of the tissue, the enzyme content is determined by photometric comparison with components of known content in the intact organ. A suitable reference component for catalase is cytochrome oxidase, the content of which in the liver is 18 nmol/g; the transition from normoxia to anoxia can be established by measuring the band at 607 nm[119]. The catalase content determined in this manner amounts to 1/3 of the content of cytochrome oxidase, *i.e.* 6 nmol/g or 24 nmol/g with respect to catalase heme (approximately 1.5 mg catalase protein per g of liver). From the data of *Price et al.*[33] and *Higashi* and *Peters*[34] results of 1 and 1.5 mg/g have been obtained. This corresponds to a catalase concentration in the peroxisome of approximately 0.5 mmol/l or 120 mg/ml.

For illustrative purposes a determination of the relative tissue content is shown in Figure 10. Here the catalase/cytochrome oxidase ratio increased from 0.33 to 1.1 because the number of peroxisomes was increased by prior treatment with ethyl 2-(*p*-chlorophenoxy)isobutyrate. This also follows from the electron micrograph of the perfused liver.

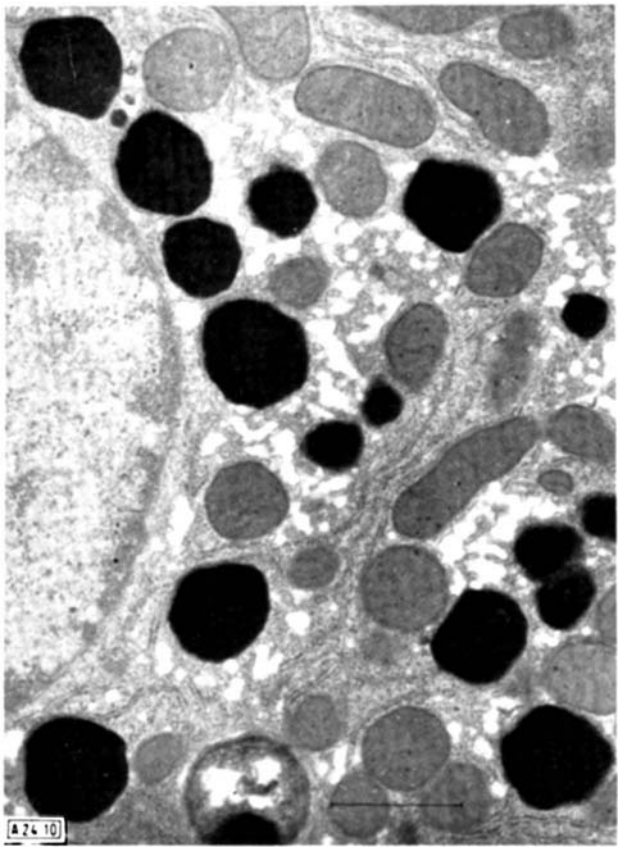


Fig. 10. Perfused liver of a rat pretreated with ethyl 2-(*p*-chlorophenoxy)isobutyrate. Bottom: Absorbance difference spectra, a) catalase minus catalase Compound I (cf. Fig. 7), b) cytochrome oxidase (through subsequent anoxia). The ratio of the catalase and cytochrome oxidase contents is 1.1 (as opposed to 0.33 for an untreated rat). Top: Electron micrograph of this liver after 1 h of perfusion. The number of peroxisomes (contrasted by the DAB reaction after [41]) has increased, while the number of mitochondria has remained unchanged (after [42]). The distance marker corresponds to 1 μm.

5. H_2O_2 Metabolism of the Liver Cell

5.1. H_2O_2 Formation

Identification of the substrates which form H_2O_2 in the liver in the endogenous steady state has not yet been performed. For example, uric acid is continuously formed from purine degradation, its concentration in rat liver amounting to 70 μmol/l[120]. In addition to urate oxidase, flavin-dependent enzyme systems come into consideration for H_2O_2 production[121], either directly or by means of the superoxide radical $O_2^{\cdot-}$[122, 123] through superoxide dismutase[124a–c]. However, the autoxidizability of flavin enzymes is quite variable, as is indicated by the distinction between flavin oxidases and flavin dehydrogenases (cf. reviews on acceptor specificities[125a, b]). In the case of xanthine oxidase a shift between oxidase and dehydrogenase activities was described[126].

Increments of H_2O_2 formation by the addition of H_2O_2-producing substrates can be determined directly by an increase in the methanol concentration required for the half-maximal decomposition of Compound I (cf. eq. (6)). The H_2O_2 formation of approximately 50 nmol min^{-1} g^{-1} determined in this

manner in the intact liver increases 10-fold in the presence of glycolate, and 15-fold in the presence of urate (Table 5). Hence it is in the order of magnitude of 1/100 to 1/10 of the total O_2 uptake. *Portwich* and *Aebi*[128] found comparable rates of H_2O_2 formation in liver slices and liver homogenates by measurement of the peroxidatic oxidation of ^{14}C-formate. The H_2O_2 concentration in the endogenous steady state is 10^{-9} mol/l and increases to 10^{-7} mol/l with maximal stimulation of the H_2O_2 formation by the substrates added[127]. Low steady state turnover numbers of $< 10\,min^{-1}$ to approximately $100\,min^{-1}$ at maximal stimulation are characteristic for the *in situ* condition. Isolated catalase is well-known for particularly high maximal turnover numbers of $> 10^8$ min^{-1}[129]. Hence catalase *in situ* operates in a region that favors the peroxidatic reaction relative to the catalatic reaction. However, this does not mean to say that at high turnover numbers the peroxidatic pathway would be inhibited. Some H_2O_2-producing enzymes of the liver are given in Table 6.

Table 5. Rate of H_2O_2 production in isolated hemoglobin-free perfused rat liver in several metabolic states. Determination by measurement of the heme occupancy [see eq. (6)] (after [127]). $\frac{1}{e} \cdot \frac{dx_n}{dt}$ = steady state turnover number, $dx_n/dt \approx H_2O_2$-formation rate.

Substrate or inhibitor	$[CH_3OH]$ at $p_M/2e$ [mmol/l]	$\frac{1}{e}\frac{dx_n}{dt}$ [min^{-1}]	$\frac{dx_n}{dt}$ [nmol/min][a]
L-Lactate 2 mmol/l, pyruvate 0.3 mmol/l	0.12 (0.09–0.16)	3.8	49
+ Antimycin A 8 µmol/l	0.18	5.8	75
+ Octanoate 0.3 mmol/l and Antimycin A 8 µmol/l	0.40	13.0	170
+ Oleate 0.1 mmol/l	0.16	5.1	66
+ Urate 1 mmol/l	—	54 [b]	750
+ Glycolate 3 mmol/l	—	34 [b]	490

[a] Per gram of liver.
[b] Titration in the presence of 0.6 mmol/l of methanol.

The question widely discussed at the beginning of this century, "Does hydrogen peroxide play any role in the living cell?" (cf. [130]), can be answered by stating that the production of H_2O_2 (as well as O_2^- and organic hydroperoxides) is a normal attribute of aerobic metabolism. A survey of the detection of H_2O_2 formation in living cells and cell fractions is given in Table 7.

The above-mentioned H_2O_2 formation rates may be regarded as the lower limits of the *in vivo* rates, because in the extraperoxisomal space other peroxidases, *e.g.* glutathione peroxidase[143, 144], can compete with catalase for H_2O_2[145]. For example, oxidized glutathione appears in the effluent perfusate after infusion of H_2O_2[146], indicating the activity of glutathione peroxidase. About 1/3 of this enzyme is localized in the mitochondrial matrix and about 2/3 in the cytosol[147].

Table 6. H_2O_2-(or O_2^--)producing enzymes of the liver and their subcellular localization.

EC number	Enzyme (trivial name)	Localization
1.1.3.1	Glycolate oxidase	Peroxisome
1.1.3.α	L-α-Hydroxy acid oxidase	Peroxisome
1.1.3.8	L-Gulonolactone oxidase	
1.2.3.1	Aldehyde oxidase	
1.2.3.2	Xanthine oxidase	Cytosol
1.4.3.3	D-Amino acid oxidase	Peroxisome
1.4.3.4	Monoamine oxidase	Mitochondrial outer membrane
1.4.3.5	Pyridoxamine oxidase	
1.4.3.6	Diamine oxidase	Endoplasmic reticulum
1.6.99.1	NADPH cytochrome c reductase	Endoplasmic reticulum
1.6.99.3	NADH cytochrome c reductase	
1.7.3.3	Urate oxidase	Peroxisome, "core"
1.15.1.1	Superoxide dismutase	Cytosol, mitochondrial matrix

Under certain experimental conditions intraperoxisomally formed H_2O_2 can also leave the peroxisomes and be detected *e.g.* by the complex with cytochrome c peroxidase from yeast.

Table 7. Detection of H_2O_2 formation in living cells and subcellular fractions.

Source	Example	Detection by	Ref.
Bacteria	*Micrococcus lysodeikticus*	Catalase Compound I	[131]
Worms	*Ascaris lumbricoides*	Polarography	[132, 133]
Blood cells	Leukocytes	Diacetyldichlorofluorescein	[134]
Liver	Liver slices and homogenates	^{14}C-Formate → $^{14}CO_2$	[128]
	Isolated perfused rat liver	Catalase Compound I	[113]
Cell fractions			
Mitochondria	Liver (rat)	Catalase Compound I	[103]
		Cytochrome c peroxidase	[137]
	Heart (pigeon)	Scopoletin, horseradish peroxidase	[135]
		Cytochrome c peroxidase	[136]
	Yeast (*S. cerevisiae*)	Cytochrome c peroxidase	[138]
	Protozoa (*C. fasciculata*)	Cytochrome c peroxidase	[139]
Microsomes	Liver (rat)	Scopoletin, horseradish peroxidase	[140]
		Cytochrome c peroxidase	[137]
Peroxisomes	Liver (rat)	Cytochrome c peroxidase	[137]
Cytosol	Liver (rat)	Cytochrome c peroxidase	[137]
Submitochondrial particles	Liver (rat)	Diacetyldichlorofluorescein	[141]
		Polarography	[142]

The increase in heme occupancy of catalase upon infusion of octanoate and antimycin A (Table 5), which is attributed to increments of mitochondrial H_2O_2 production in the liver[127], is therefore particularly striking.

From experiments conducted so far on subcellular fractions[141,99,135-137] it follows that the mitochondrial H_2O_2 production depends on the control state[99] and is greatest[99,135] in the state of respiratory control by the availability of phosphate acceptor ("State 4"[148]). The segment succinate-cytochrome b_{566} as well as the system of energy conservation are postulated to play a role in H_2O_2 formation[149,136]. Since in this segment of the respiratory chain the transition from two-electron transfer to one-electron transfer takes place, the primary product could also be the superoxide radical O_2^-, which then dismutates into H_2O_2 and O_2. Experimental support for this possibility has been provided by *Loschen et al.*[150].

An increase in the oxygen pressure from atmospheric to 1.92 MPa (19 atm) increases the rate of H_2O_2 formation fourfold in pigeon heart mitochondria and 15- to 20-fold in rat liver mitochondria[136]. Thus, considerable differences should exist in the oxygen affinity of the H_2O_2-producing systems. Recently *Oshino et al.*[151a] were able to demonstrate *in situ* on anesthetized rats a fourfold increase of H_2O_2 production in the liver in the presence of glycolate when the animal was exposed to oxygen pressures of 1 atm.

A source of H_2O_2 that is normally negligible but which is worth mentioning is high-energy radiation. X-irradiation of neutral aqueous solutions produces H_2O_2 as a stable product in a concentration of approximately 3—4 $\mu mol\,l^{-1}\,kR^{-1}$[152,153].

5.2. Hydrogen Donors for the Peroxidatic Reaction

The peroxidatic reaction, the "coupled oxidation" of *Keilin* and *Hartree*[77,78], *i.e.* the combination of reactions (1a) and (1c), is important for the metabolism of a number of hydrogen donors in the liver, and thus for methanol[13,154-157], ethanol[158], nitrite[159], and formate[160]. From the reaction sequence it follows that the rate of the oxidation of the hydrogen donors in the steady state cannot be greater than the rate of formation of hydrogen peroxide. With the exception of extremely high hydrogen donor concentrations, however, this value is not reached, as the catalase reaction competes with the peroxidatic reaction (cf. Figure 5)[105]. It should be mentioned that high donor concentrations can be obtained by exogenous supply (50 mmol of ethanol/l ≙ 2.3 ‰).

The titration curves of the steady heme occupancy of catalase in the perfused liver are different for the two primary alcohols methanol and ethanol (Figure 11). On the addition of 4-methylpyrazole the difference disappears; hence, this difference must be attributed to the activity of the alcohol dehydrogenase[127]. The titration curve for methanol remains unchanged on the addition of 4-methylpyrazole—an indication of the lack of reactivity of methanol with the dehydrogenase. These observations are in accord with the similarity of the rate constants k_4 in the reaction of catalase with methanol and ethanol[13].

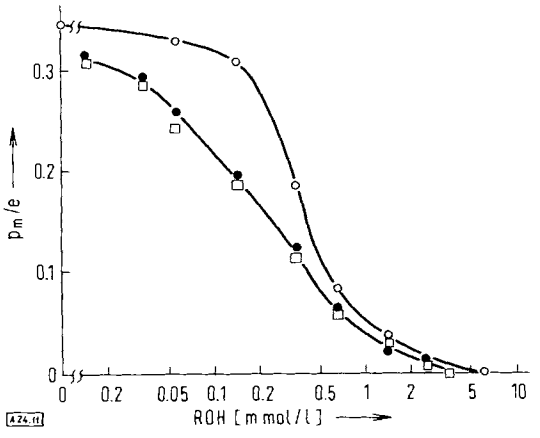


Fig. 11. Dependence of the heme occupancy of catalase (p_m/e) on methanol (□) and ethanol concentration in the perfusate (ROH). The ethanol titration was carried out in the presence (●) and in the absence (○) of 0.1 mmol/l of 4-methylpyrazole (after [127]).

The oxidation of ethanol *via* the catalase pathway is stimulated by increased H_2O_2 formation, as shown in Figure 12. By glycolate addition in the presence of methylpyrazole, the oxidation of ethanol per g of liver increases by approximately

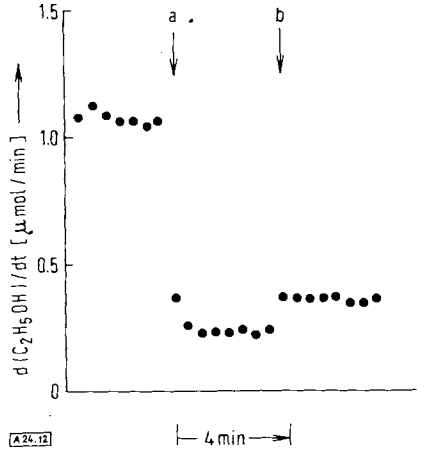


Fig. 12. Ethanol uptake by perfused rat liver, per g of liver [2 mmol of ethanol per l of influent perfusate]. Ethanol uptake in the presence of 90 µmol/l of 4-methylpyrazole (added at point a) is 22% of the control value and increases after the addition of 3.8 mmol/l of glycolate (at point b) to 34%. This increase corresponds, per g of liver, to about 150 nmol/min (after [161]).

150 nmol/min. The stimulation of H_2O_2 production per g liver under these conditions is approximately 400 nmol/min, so that about 35—40% of the H_2O_2 additionally produced is used for the peroxidatic reaction. As expected, this proportion increases at higher ethanol concentrations[162]. The rate of the oxidation of methanol also increases on addition of glycolate[163]. Since the peroxidatic oxidation of ethanol is not connected with NAD^+ reduction, this pathway can be of use[116,164] for avoiding the negative shift caused by the alcohol dehydrogenase in the redox potential of the cytosolic free NAD^+ system[165-169].

Currently, the possibility is being considered whether this could be utilized to influence liver metabolism in alcoholism. *Blomstrand* and *Kager*[170] demonstrated on human subjects that the inhibition of fatty acid oxidation and the accumulation of triglycerides by ethanol can be largely suppressed by the addition of 4-methylpyrazole. Therefore, the use of pyrazole

derivatives concomitant with a stimulation of the peroxidatic pathway of ethanol oxidation opens interesting perspectives. According to recent studies, the peroxidatic oxidation of ethanol by catalase should be responsible[105,137,140,174] for the activity of a special "microsomal ethanol-oxidizing system" (MEOS)[171-173]. The NADPH-specificity of the microsomal activity is attributed in this case to the coenzyme specificity of an autoxidizable microsomal flavoprotein[137,175]. Should this explanation be correct, the oxidation of ethanol in intact endoplasmic reticulum without catalase should not play a physiologically important role (for discussion, see [176]).

Of the aldehydes, catalase only acts on formaldehyde; acetaldehyde is not oxidized[177]. Hence, by measuring catalase Compound I one can follow the formation of ethanol from acetaldehyde[178] in the liver[171].

The question of the nature of the endogenous hydrogen donors is still largely unsettled. Only for ethanol has a continuous supply from the intestinal tract of rats been verified by determinations in portal and in caval blood[179]. Methanol can be formed continuously with the help of pectase by hydrolytic cleavage from pectins; in this manner in human subjects approximately 10–20 mmol of methanol are set free per day[180].

deDuve and *Baudhuin*[12] postulated that the peroxidatic oxidation of α-hydroxy acids plays a role in gluconeogenesis since it might be linked to an oxidation of extramitochondrial reducing equivalents (NADH). Experimental proof of this hypothesis is still lacking.

The possible function of catalase in lipid metabolism of the liver, as already postulated by *Novikoff* and *Shin*[54] and also suggested by the effects of the hypolipidemically active drugs, also remains obscure. Acatalasemic strains of mice as compared to wild strains contain a diminished serum concentration of triglycerides and cholesterol[181]. A possible reason for this observation could reside in a higher content of catalase degradation products within the peroxisomes. It is known that acatalasemia in mice can be attributed to a thermolabile variant of catalase[182], possibly resulting in an increased level of degradation products (*e.g.* subunits). A fall in the blood lipids was produced experimentally by injection of catalase subunits with peroxidatic activity[183-185]. Recently, the lack of peroxisomes in the liver, which contained considerable lipid deposits, was described in a human patient with a fatal cerebro-hepato-renal syndrome (Zellweger's disease)[186].

6. Outlook

The methods of acquiring biochemical information on intracellular processes in intact surviving organs allow insight into the metabolism of hydrogen peroxide taking place in the range of nanomolar concentrations. Constant production of H_2O_2 is a normal feature of liver metabolism. Exogenous influences, *e.g.* the effects of radiation[187,188] or oxygen and ozone poisoning[189,190], could not be discussed here in detail.

Corresponding to our still limited knowledge of the metabolism of endogenous H_2O_2-producing substrates and the endogenous hydrogen donors, we are still at the beginning of a full comprehension of the function of liver catalase (cf.[12,18,20]). Also, phenomena such as the decreased activity of catalase in tumor cells[191] and the inhibition of catalase activity by tumor extracts[192], which is reported to be based upon formation of Compound II[193,194], still require clarification. In contrast, for the plant variants of peroxisomes, *e.g.* the glyoxysomes, clear concepts already exist regarding their function in fat and carbohydrate metabolism (glyoxylate cycle), as well as in photorespiration and photosynthesis (reviews in [17,195]). In particular, the implication attached to the term peroxisome requires further elucidation for animal tissue cells. With the steadily increasing number of known enzyme activities in peroxisomes and peroxisome-containing cell types with biphenyltetramine oxidase activity (cf. the peroxisomes in the small intestine[196] and the myocardium[197,198], in steroid-secreting cells such as the interstitial cells (Leydig cells) of the testes[199] and the adrenal cortex[200]) and with the rapid development of biochemical and cytological methods, further aspects are expected in the near future on the cell biology of catalase, which was once described as a "fossil enzyme"[18].

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[1] *J. Rhodin*: Correlation of Ultrastructural Organization and Function in Normal and Experimentally Changed Convoluted Tubule Cells of the Mouse Kidney. Aktiebolaget Godvil, Stockholm 1954.

[2] *C. Rouiller* and *W. Bernhard*, J. Biophys. Biochem. Cytol. *2*, Suppl. 355 (1956).

[3] *W. C. Schneider* and *G. H. Hogeboom*, J. Biol. Chem. *195*, 161 (1952).

[4] *K. Paigen*, J. Biol. Chem. *206*, 945 (1954).

[5] *J. F. Thomson* and *F. J. Klipfel*, Arch. Biochem. Biophys. *70*, 224 (1957).

[6] *D. H. Adams* and *E. A. Burgess*, Brit. J. Cancer *11*, 310 (1957).

[7] *C. deDuve, B. C. Pressman, R. Gianetto, R. Wattiaux*, and *F. Appelmans*, Biochem. J. *60*, 604 (1955).

[8] *C. deDuve, R. Wattiaux*, and *P. Baudhuin*, Advan. Enzymol. *24*, 291 (1962).

[9] *P. Baudhuin, H. Beaufay*, and *C. deDuve*, J. Cell Biol. *26*, 219 (1965).

[10] *F. Leighton, B. Poole, H. Beaufay, P. Baudhuin, J. W. Coffey, S. Fowler*, and *C. deDuve*, J. Cell Biol *37*, 482 (1968).

[11] *C. deDuve*, J. Cell Biol. *27*, 25A (1965).

[12] *C. deDuve* and *P. Baudhuin*, Physiol. Rev. *46*, 323 (1966).

[13] *B. Chance*, Acta Chem. Scand. *1*, 236 (1947).

[14] *J. F. Hogg*, Ann. N. Y. Acad. Sci. *168*, 209 (1969).

[15] *H. Hruban* and *M. Rechcigl*, Int. Rev. Cytol. Suppl. I (1969).

[16] *P. Baudhuin* in *A. Lima-de-Faria*: Handbook of Molecular Cytology. North Holland, Amsterdam 1969, p. 1179.

[17] *N. E. Tolbert* in *D. D. Davies*: Rate Control of Biological Processes. Cambridge University Press 1973, p. 215.

[18] *P. Nicholls* and *G. R. Schonbaum* in *P. Boyer, H. A. Lardy*, and *K. Myrbäck*: The Enzymes. 2nd Edit., Academic Press, New York 1963, Vol. 8, p. 147.

[19] *A. S. Brill* in *M. Florkin* and *E. H. Stotz*: Comprehensive Biochemistry. Elsevier, Amsterdam 1966, Vol. 13, p. 447.

[20] *A. Deisseroth* and *A. L. Dounce*, Physiol. Rev. *50*, 319 (1970).

[21] *Z. Hruban* and *H. Swift*, Science *146*, 1316 (1964).

[22] *R. Wattiaux, M. Wibo*, and *R. Baudhuin* in: Ciba Foundation Symposium on Lysosomes. Churchill, London 1963, p. 176.

[23] *P. Baudhuin*, Ann. N. Y. Acad. Sci. *168*, 214 (1969).

[24] *D. deDuve*, Ann. N. Y. Acad. Sci. *168*, 369 (1969).

[25] *F. Leighton, B. Poole, P. B. Lazarow*, and *C. deDuve*, J. Cell Biol. *41*, 521 (1969).

[26] *R. Gee, E. McGroarty, B. Hsieh, D. M. Wied*, and *N. E. Tolbert*, Arch. Biochem. Biophys. *161*, 187 (1974).

[27] *E. McGroarty, B. Hsieh, D. M. Wied, R. Gee*, and *N. E. Tolbert*, Arch. Biochem. Biophys. *161*, 194 (1974).

[28] *M. A. K. Markwell, E. McGroarty, L. L. Bieber*, and *N. E. Tolbert*, J. Biol. Chem. *248*, 3426 (1973).

[29] *R. P. Donaldson, N. E. Tolbert*, and *C. Schnarrenberger*, Arch. Biochem. Biophys. *152*, 199 (1972).

[30] *E. R. Weibel, W. Stäubli, H. R. Gnägi*, and *F. A. Hess*, J. Cell Biol. *42*, 68 (1969).

[31] *C. deDuve*, Harvey Lect. *59*, 49 (1965).

[32] *B. Poole, F. Leighton*, and *C. deDuve*, J. Cell Biol. *41*, 536 (1969).

[33] *V. E. Price, W. R. Sterling, V. A. Tarantola, R. W. Hartley*, and *M. Rechcigl*, J. Biol. Chem. *237*, 3468 (1962).

[34] *T. Higashi* and *T. Peters*, J. Biol. Chem. *238*, 3945 (1963).

[35] *G. Brunner* and *W. Neupert*, FEBS Lett. *1*, 153 (1968).

[36] *T. Omura, P. Siekevitz*, and *G. Palade*, J. Biol. Chem. *242*, 2389 (1967).

[37] *T. K. Shnitka* and *A. M. Seligman*, Annu. Rev. Biochem. *40*, 375 (1971).

[38] *R. C. Graham* and *M. J. Karnovsky*, J. Histochem. Cytochem. *14*, 291 (1966).

[39] *A. B. Novikoff* and *S. Goldfischer*, J. Histochem. Cytochem. *16*, 507 (1968).

[40] *H. D. Fahimi*, J. Histochem. Cytochem. *16*, 547 (1968).

[41] *P. G. Legg* and *R. L. Wood*, J. Cell Biol. *45*, 118 (1970).

[42] *H. Sies, V. Herzog*, and *F. Miller*, Proc. Fifth Eur. Congr. Electron Microscopy *1972*, 274.

[43] *V. Herzog* and *H. D. Fahimi*, J. Cell Biol. *60*, 303 (1974).

[44] *S. Marklund*, Biochim. Biophys. Acta *321*, 90 (1973).

[45] *R. S. Holmes* and *C. J. Masters*, Arch. Biochem. Biophys. *148*, 217 (1972).

[46] *D. J. Svoboda* and *D. L. Azarnoff*, Fed. Proc. *30*, 841 (1971).

[47] *D. J. Svoboda* and *D. L. Azarnoff*, J. Cell Biol. *30*, 442 (1966).

[48] *W. Stäubli* and *R. Hess* in *R. Uyeda:* Electron Microscopy. Vol. 2. Maruzen, Tokyo 1966, p. 625.

[49] *J. Reddy, M. Chiga*, and *D. Svoboda*, Biochem. Biophys. Res. Commun. *43*, 318 (1971).

[50] *D. Azarnoff* and *D. R. Tucker*, Fed. Proc. *25*, 388 (1965).

[51] *T. P. Krishnakantha* and *C. K. Kurup*, Biochem. J. *130*, 167 (1972).

[52] *Z. Hruban, H. Swift*, and *A. Slesers*, Lab. Invest. *15*, 1884 (1966).

[53] *J. Reddy, M. Chiga, S. Bunyaratvej*, and *D. Svoboda*, J. Cell Biol. *44*, 226 (1970).

[54] *A. B. Novikoff* and *W. Y. Shin*, J. Microsc. *3*, 187 (1964).

[55] *C. deDuve*, J. Histochem. Cytochem. *21*, 941 (1973).

[56] a) *P. B. Lazarow*, and *D. deDuve*, Biochem. Biophys. Res. Commun. *45*, 1198 (1971); b) J. Cell Biol. *59*, 491, 507 (1973).

[57] *A. Nakamura, T. Hara*, and *S. Minakami*, J. Biochem. *73*, 47 (1973).

[58] *A. Nakamura* and *S. Minakami*, J. Biochem. *74*, 683 (1973).

[59] *A. M. Novikoff* and *A. B. Novikoff*, J. Cell Biol. *53*, 532 (1972).

[60] *H. D. Fahimi*, J. Histochem. Cytochem. *21*, 999 (1973).

[61] *K. Kashiwagi, T. Tobe*, and *T. Higashi*, J. Biochem. *70*, 785 (1971).

[62] a) *T. Sakamoto* and *T. Higashi*, J. Biochem. *73*, 1083 (1973); b) *M. Takagi, T. Tanaka*, and *K. Ogata*, *ibid. 65*, 651 (1969).

[63] *T. Higashi* and *T. Peters*, J. Biol. Chem. *238*, 3952 (1963).

[64] *C. M. Redman, D. J. Grab*, and *R. Irukulla*, Arch. Biochem. Biophys. *152*, 496 (1972).

[65] *K. Uenoyama* and *T. Ono*, J. Mol. Biol. *65*, 75 (1972).

[66] *L. J. Thénard*, l'Academie des Sciences, Paris 1818; cf. *L. J. Thénard:* Traite de Chimie. 6th Edit., Vol. I. Ed. Crochard, Paris 1834, p. 529.

[67] *O. Loew*, U. S. Dep. Agr. Report No. 68 (1901).

[68] *C. F. Schönbein*, J. Prakt. Chem. *98*, 339 (1863).

[69] *J. Jacobsen*, Hoppe-Seylers Z. Physiol. Chem. *16*, 340 (1892).

[70] *O. Warburg*, Biochem. Z. *136*, 266 (1923).

[71] *O. Warburg:* Schwermetalle als Wirkungsgruppen von Fermenten. Editio Cantor, Freiburg 1949.

[72] *H. Wieland*, Liebigs Ann. Chem. *445*, 181 (1925).

[73] *H. v. Euler* and *K. Zeile* in *H. v. Euler:* Chemie der Enzyme. Part II. Verlag Bergmann, München 1934, Section 3, p. 1.

[74] a) *J. B. Sumner* and *A. L. Dounce*, Science *85*, 366 (1937); b) *H. Theorell*, Enzymologia *10*, 25 (1942).

[75] *B. Chance* in *J. B. Sumner* and *K. Myrbäck:* The Enzymes. Vol. II, Part 1. Academic Press, New York 1951, p. 428.

[76] *H. Theorell* in *J. B. Sumner* and *K. Myrbäck:* The Enzymes. Vol. II, Part 1. Academic Press, New York 1951, p. 397.

[77] *D. Keilin* and *E. F. Hartree*, Proc. Roy. Soc. *B 119*, 141 (1936).

[78] *D. Keilin* and *E. F. Hartree*, Biochem. J. *39*, 293 (1945).

[79] *B. Chance, D. S. Greenstein*, and *F. J. W. Roughton*, Arch. Biochem. Biophys. *37*, 300 (1952).

[80] *B. Chance*, J. Biol. Chem. *179*, 1341 (1949).

[81] *A. S. Brill* and *R. J. P. Williams*, Biochem. J. *78*, 253 (1961).

[82] *H. Sies, T. Bücher, N. Oshino*, and *B. Chance*, Arch. Biochem. Biophys. *154*, 106 (1973).

[83] *P. George* in *D. E. Green:* Currents in Biochemical Research. Interscience, New York 1956, p. 338.

[84] *G. R. Schonbaum* and *S. Lo*, J. Biol. Chem. *247*, 3353 (1972).

[85] *P. Jones* and *D. N. Middlemiss*, Biochem. J. *130*, 411 (1972).

[86] *G. R. Schonbaum*, Abstr. Wenner-Gren Symp. Stockholm 1970, p. 48.

[87] *N. Oshino, B. Chance*, and *H. Sies*, Arch. Biochem. Biophys. *159*, 704 (1973).

[88] *D. Keilin* and *P. Nicholls*, Biochim. Biophys. Acta *29*, 302 (1958).

[89] *K. Zeile* and *H. Hellström*, Hoppe-Seylers Z. Physiol. Chem. *192*, 171 (1930).

[90] *B. Chance*, J. Biol. Chem. *179*, 1299 (1949).

[91] *D. Keilin* and *E. F. Hartree*, Biochem. J. *39*, 148 (1945).

[92] *H. Theorell* and *A. Ehrenberg*, Arch. Biochem. Biophys. *41*, 442 (1952).

[93] *P. Nicholls*, Biochem. J. *90*, 331 (1964).

[94] *W. G. Heim, D. Appleman*, and *H. T. Pyfrom*, Amer. J. Physiol. *186*, 19 (1956).

[95] *E. Margoliash* and *A. Novogrodsky*, Biochem. J. *68*, 468 (1958).

[96] *B. B. L. Agrawal, E. Margoliash, M. I. Levenberg, R. S. Egan*, and *M. H. Studier*, Fed. Proc. *29*, 732 A (1970).

[97] *E. Margoliash, A. Novogrodsky*, and *A. Schejter*, Biochem. J. *74*, 339 (1960).

[98] *P. Nicholls*, Biochim. Biophys. Acta *59*, 414 (1962).

[99] *B. Chance* and *N. Oshino*, Biochem. J. *122*, 225 (1971).

[100] *M. Kremer*, Biochim. Biophys. Acta *198*, 199 (1970).

[101] *B. Chance* and *G. R. Schonbaum*, J. Biol. Chem. *237*, 2391 (1962).

[102] *E. Zidoni* and *M. L. Kremer*, Arch. Biochem. Biophys. *161*, 658 (1974).

[103] *B. Chance* and *N. Oshino*, Biochem. J. *131*, 564 (1973).

[104] *H. Laser*, Biochem. J. *61*, 122 (1955).

[105] *N. Oshino, R. Oshino*, and *B. Chance*, Biochem. J. *131*, 555 (1973).

[106] *H. Schnitger, R. Scholz, T. Bücher*, and *D. W. Lübbers*, Biochem. Z. *341*, 334 (1965).

[107] *D. W. Lübbers, M. Kessler, R. Scholz*, and *T. Bücher*, Biochem. Z. *341*, 346 (1965).

[108] *R. Scholz* and *T. Bücher* in *B. Chance, R. W. Estabrook* and *J. R. Williamson:* Control of Energy Metabolism. Academic Press, New York 1965, p. 393.

[109] *B. Brauser*, Z. Anal. Chem. *237*, 8 (1968).

[110] *B. Chance* and *C. M. Connelly*, Nature *179*, 1235 (1957).

[111] *J. Ramirez*, J. Physiol. *147*, 14 (1959).

[112] *F. Jöbsis*, J. Gen. Physiol. *46*, 905 (1963).

[113] *B. Chance, D. Mayer*, and *L. Rossini*, IEEE Trans. Bio-Med. Eng. *17*, 118 (1970).

[114] *B. Brauser, T. Bücher, H. Sies*, and *H. Versmold* in *K. Gaede, B. L. Horecker*, and *W. J. Whelan:* Molecular Basis of Biological Activity. Academic Press, New York 1972, p. 197.

[115] *H. Sies* and *B. Brauser*, Eur. J. Biochem. *15*, 531 (1970).

[116] *H. Sies* and *B. Chance*, FEBS Lett. *11*, 172 (1970).

[117] *H. Sies*, Fed. Proc. *30*, 1132 A (1971).

[118] *W. Niesel, D. W. Lübbers, D. Schneewolf, J. Richter*, and *W. Botticher*, Rev. Sci. Instrum. *35*, 578 (1964).

[119] *B. Brauser, H. Sies*, and *T. Bücher*, FEBS Lett. *2*, 167 (1969).

[120] *V. Eggleston* and *H. A. Krebs*, Biochem. J. *138*, 425 (1974).

[121] *O. Warburg* and *W. Christian*, Biochem. Z. *266*, 377 (1933).

[122] *I. Fridovich* and *P. Handler*, J. Biol. Chem. *236*, 1836 (1961).

[123] *V. Massey, S. Strickland, S. G. Mayhew, L. G. Howell, P. C. Engel, R. G. Matthews, M. Schuman,* and *P. A. Sullivan,* Biochem. Biophys. Res. Commun. *36*, 891 (1969).

[124] a) *J. M. McCord* and *I. Fridovich,* J. Biol. Chem. *244*, 6049 (1969); b) *I. Fridovich* in *O. Hayaishi:* Molecular Mechanisms of Oxygen Activation. Academic Press, New York 1974, p. 453; c) *U. Weser,* Struct. Bonding *17*, 1 (1973).

[125] a) *P. Hemmerich, G. Nagelschneider,* and *C. Veeger,* FEBS Lett. *8*, 69 (1970); b) *M. Dixon,* Biochim. Biophys. Acta *226*, 269 (1971).

[126] *F. Stirpe* and *E. DellaCorte,* J. Biol. Chem. *244*, 3855 (1969).

[127] *N. Oshino, B. Chance, H. Sies,* and *T. Bücher,* Arch. Biochem. Biophys. *154*, 117 (1973).

[128] *F. Portwich* and *H. Aebi,* Helv. Physiol. Acta *18*, 1 (1960).

[129] *Y. Ogura,* Arch. Biochem. Biophys. *57*, 288 (1955).

[130] *F. Battelli* and *L. Stern,* Ergeb. Physiol. *12*, 96 (1912).

[131] *B. Chance,* Science *116*, 202 (1952).

[132] *E. Bueding* and *B. Charms,* J. Biol. Chem. *196*, 615 (1952).

[133] *K. S. Cheah* and *B. Chance,* Biochim. Biophys. Acta *223*, 55 (1970).

[134] *B. Paul* and *A. J. Sbarra,* Biochim. Biophys. Acta *156*, 168 (1968).

[135] *G. Loschen, L. Flohé,* and *B. Chance,* FEBS Lett. *18*, 261 (1971).

[136] *A. Boveris* and *B. Chance,* Biochem. J. *134*, 707 (1973).

[137] *A. Boveris, N. Oshino,* and *B. Chance,* Biochem. J. *128*, 617 (1972).

[138] *M. Erecinsca, N. Oshino, P. Loh,* and *E. Brocklehurst,* Biochim. Biophys. Acta *292*, 1 (1973).

[139] *J. P. Kusel, A. Boveris,* and *B. T. Storey,* Arch. Biochem. Biophys. *158*, 799 (1973).

[140] *R. G. Thurman, H. G. Ley,* and *R. Scholz,* Eur. J. Biochem. *25*, 420 (1972).

[141] *P. C. Hinkle, R. A. Butow, E. Racker,* and *B. Chance,* J. Biol. Chem. *242*, 5169 (1967).

[142] *P. K. Jensen,* Biochim. Biophys. Acta *122*, 157 (1966).

[143] *G. C. Mills,* J. Biol. Chem. *229*, 189 (1957); Arch. Biochem. Biophys. *86*, 1 (1960).

[144] *L. Flohé,* Klin. Wochenschr. *49*, 669 (1971).

[145] *P. Hochstein* and *H. Utley,* Mol. Pharmacol. *4*, 574 (1968).

[146] a) *H. Sies, C. Gerstenecker, H. Menzel,* and *L. Flohé,* FEBS Lett. *27*, 171 (1972); b) *H. Sies, C. Gerstenecker, K. H. Summer, H. Menzel,* and *L. Flohé* in *L. Flohé, H. C. Benöhr H. Sies, H. D. Waller,* and *A. Wendel:* Glutathione. Thieme, Stuttgart 1974, p. 261.

[147] *L. Flohé* and *W. Schlegel,* Hoppe-Seylers Z. Physiol. Chem. *352*, 1401 (1971).

[148] *B. Chance* and *G. R. Williams,* J. Biol. Chem. *217*, 409 (1955).

[149] *G. Loschen, A. Azzi,* and *L. Flohé,* FEBS Lett. *33*, 84 (1973).

[150] *G. Loschen, A. Azzi, G. Richter,* and *L. Flohé,* FEBS Lett. *42*, 68 (1974).

[151] *B. Chance, N. Oshino, T. Sugano,* and *D. Jamieson* in *R. G. Thurman, T. Y. Yonetani, J. R. Williamson,* and *B. Chance:* Alcohol and Aldehyde Metabolizing Systems. Academic Press, New York 1974, p. 169.

[151a] *N. Oshino, D. Jamieson, T. Sugano,* and *B. Chance,* Biochem. J., in press.

[152] *H. Aebi, A. Temperli, R. Gressly, R. Oestreicher,* and *A. Zuppinger,* Helv. Chim. Acta *18*, 1714 (1960).

[153] *H. Aebi,* Radiat. Res. Suppl. *3*, 130 (1963).

[154] *H. Aebi, E. Frei, R. Knab,* and *P. Siegenthaler,* Helv. Physiol. Acta *15*, 150 (1957).

[155] *T. R. Tephly, R. E. Parks,* and *G. J. Mannering,* J. Pharmacol. Exp. Ther. *143*, 292 (1964).

[156] *D. R. Van Harken, T. R. Tephly,* and *G. J. Mannering,* J. Pharmacol. Exp. Ther. *149*, 36 (1965).

[157] *T. R. Tephly, W. D. Watkins,* and *J. I. Goodman:* Essays in Toxicology. Vol. 5. Academic Press, New York 1974, p. 149.

[158] *E. Jacobsen,* Nature *169*, 645 (1952).

[159] *L. A. Heppel* and *V. T. Porterfield,* J. Biol. Chem. *178*, 549 (1949).

[160] *H. Aebi, H. Koblet,* and *J. P. von Wartburg,* Helv. Physiol. Acta *15*, 384 (1957).

[161] *H. Sies* in *R. G. Thurman, T. Y. Yonetani, J. R. Williamson,* and *B. Chance:* Alcohol and Aldehyde Metabolizing Systems. Academic Press, New York 1974, p. 183.

[162] *R. G. Thurman,* Fed. Proc. *32*, 1510 (1973).

[163] *G. J. Mannering, D. R. Van Harken, A. B. Makar, T. R. Tephly, W. D. Watkins,* and *J. I. Goodman,* Ann. N. Y. Acad. Sci. *168*, 265 (1969).

[164] *H. Theorell, B. Chance, T. Yonetani,* and *N. Oshino,* Arch. Biochem. Biophys. *151*, 434 (1972).

[165] *H. A. Krebs,* Advan. Enzyme Regul. *6*, 467 (1968).

[166] *T. Bücher* in *H. Sund:* Pyridine Nucleotide Dependent Dehydrogenases. Springer, Berlin 1970, p. 439.

[167] *J. R. Williamson, R. Scholz, E. T. Browning, R. G. Thurman,* and *M. H. Fukami,* J. Biol. Chem. *244*, 5044 (1969).

[168] *G. A. Martini* and *C. Bode:* Metabolic Changes Induced by Alcohol. Springer, Berlin 1971.

[169] *R. Blomstrand* and *H. Theorell,* Life Sci. *10*, 631 (1970).

[170] *R. Blomstrand* and *L. Kager* in *R. G. Thurman, T. Y. Yonetani, J. R. Williamson,* and *B. Chance:* Alcohol and Aldehyde Metabolizing Systems. Academic Press, New York 1974, p. 339.

[171] *W. J. Orme-Johnson* and *D. M. Ziegler,* Biochem. Biophys. Res. Commun. *21*, 78 (1965).

[172] *C. S. Lieber* and *L. M. DeCarli,* J. Biol. Chem. *245*, 2505 (1970).

[173] *R. Teschke, Y. Hasumura, J. G. Joly, H. Ishii,* and *C. S. Lieber,* Biochem. Biophys. Res. Commun. *49*, 1187 (1972).

[174] *E. Feytmans* and *F. Leighton,* Biochem. Pharmacol. *22*, 349 (1973).

[175] *J. R. Gillette, B. B. Brodie,* and *B. N. LaDu,* J. Pharmacol. Exp. Ther. *119*, 532 (1957).

[176] *R. G. Thurman, T. Y. Yonetani, J. R. Williamson,* and *B. Chance:* Alcohol and Aldehyde Metabolizing Systems. Academic Press, New York 1974.

[177] *B. Chance,* J. Biol. Chem. *182*, 649 (1950).

[178] *K. O. Lindros, R. Vihma,* and *O. A. Forsander,* Biochem. J. *126*, 945 (1972).

[179] *H. A. Krebs* and *J. R. Perkins,* Biochem. J. *118*, 635 (1970).

[180] *H. Aebi,* personal communication.

[181] *S. Goldfischer, P. S. Roheim, D. Edelstein,* and *E. Essner,* Science *173*, 65 (1971).

[182] *H. Aebi, H. Suter,* and *R. N. Feinstein,* Biochem. Genet. *2*, 245 (1968).

[183] *J. Caravaca, M. D. May,* and *E. G. Dimond,* Biochem. Biophys. Res. Commun. *10*, 189 (1963).

[184] *J. Caravaca* and *M. D. May,* Biochem. Biophys. Res. Commun. *16*, 528 (1964).

[185] *J. Caravaca, E. G. Dimond, S. C. Sommers,* and *R. Wenk,* Science *155*, 1284 (1967).

[186] *S. Goldfischer, C. L. Moore, A. B. Johnson, A. J. Spiro, M. P. Valsamis, K. K. Wisniewski, R. H. Ritch, W. T. Norton, I. Rapin,* and *L. Gartner,* Science *182*, 62 (1973).

[187] *R. N. Feinstein,* Radiat. Res. Suppl. *3*, 1 (1963).

[188] *W. Bors, M. Saran, E. Lengfelder, R. Spöttl,* and *C. Michel,* Curr. Top. Radiat. Res. Quart. *9*, 247 (1974).

[189] *R. Gerschman* in *F. Dickens* and *E. Neil:* Oxygen in the Animal Organism. Pergamon, Oxford 1964, p. 475.

[190] *D. B. Menzel,* Annu. Rev. Pharmacol. *10*, 379 (1970).

[191] *O. Warburg, K. Gawehn, A. W. Geissler, W. Schröder, H. Gewitz,* and *W. Volker,* Arch. Biochem. Biophys. *78*, 573 (1958).

[192] *A. Seabra* and *H. F. Deutsch,* J. Biol. Chem. *214*, 447 (1955).

[193] *N. M. Alexander,* J. Biol. Chem. *227*, 975 (1957).

[194] *E. Margoliash* and *A. Novogrodsky,* Biochim. Biophys. Acta *30*, 182 (1958).

[195] *N. E. Tolbert,* Annu. Rev. Plant Physiol. *22*, 45 (1971).

[196] *P. M. Novikoff* and *A. B. Novikoff,* J. Cell Biol. *53*, 532 (1972).

[197] *V. Herzog* and *H. D. Fahimi,* Science *185*, 271 (1974).

[198] *A. R. Hand,* J. Histochem. Cytochem. *22*, 207 (1974).

[199] *J. Reddy* and *D. Svoboda,* Lab. Invest. *26*, 657 (1972).

[200] *V. H. Black* and *B. I. Bogart,* J. Cell Biol. *57*, 345 (1973).

Specific Interactions. Intermolecular Forces, Steric Requirements, and Molecular Size

By Zeno Simon[*]

Specific interactions or recognition processes are extremely important in many fields of chemistry and biology: typical examples are the enzyme-substrate and the antigen-antibody reactions. Quantitative predictions require a knowledge of steric fit, intermolecular forces, and molecular size. These considerations should facilitate design of new drugs.

1. Introduction

The specificity problem was probably first encountered by the analytical chemist searching for a reagent to precipitate a particular cation out of a mixture. It became a matter of everyday concern to the biochemist, and especially the medicinal chemist, with the advent of *Emil Fischer*'s[1] "lock-and-key" theory of enzyme-substrate interaction, *Paul Ehrlich*'s search for "magic bullets" to kill bacteria without harming the organism, and the study of immune reactions[2].

The specificity or recognition problem is concerned with the fact that a certain molecule A_0—let us term it recognizer—combines with or precipitates only a certain molecular "effector" B_0 out of a sometimes very large number N of such possible effectors B_i. For example, an antibody usually recognizes only the antigenic determinant by which it was elicited, but not the antigenic determinants of the organism's proteins. Likewise an enzyme catalyzes the reaction of only one molecule (*i. e.* its substrate) out of several similar available molecules.

Such specific interactions imply a high affinity of A_0 for B_0 and a sufficiently lowered one for the "false partners" B_i; this idea was implicit in the first attempts to obtain specific reagents, and as early as 1907 *Arrhenius* described immune reactions in terms of chemical equilibria[3]. Thereafter, systematic searches for steric fit requirements and types of forces involved seem to have been conducted mostly by chemists concerned with immune reactions (see, *e. g.*, ref.[4]) and catalysts[5], although much experimental work was also performed in the fields of medicinal chemistry, enzymology, and analytical chemistry. The chemotherapeutic arsenal, industrial catalysts, and the complexons of analytical chemistry are some of the results of this work.

The link between molecular size and specificity may have been recognized less clearly during this work. The earliest reagents used in analytical chemistry—the sulfide ion (S^{2-}) and the carbonate ion (CO_3^{2-})—have low molecular weights and precipitate about half of the several hundred known cations; hence separation of a given cation requires several successive "selection" procedures. Ethylenediaminetetraacetic acid, *Paul Ehrlich*'s Salvarsan, and the sulfonamides, have molecular weights of several hundred. Antibiotics reach molecular weights near 1000, while repressors like the lac repressor, which binds specifically at a certain nucleotide sequence in the *E. coli* genome[6], are proteins (see Fig. 1).

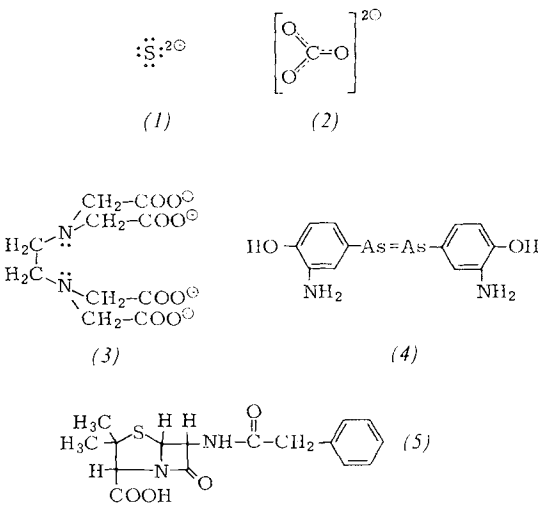


Fig. 1. Molecules of various size and specificity: sulfide ion, *(1)*; carbonate ion, *(2)*; ethylenediaminetetraacetate ion, *(3)*; Salvarsan, *(4)*; penicillin G, *(5)*.

Attempts to characterize quantitatively specific interactions, to relate specificity to affinity differences and molecular size are confined to the last few years. The probability of false base incorporation in DNA replication and transcription was related to affinity differences by *Volkenshtein* and *Eliashevich*[7], specificity-molecular size relations were discussed in relation to DNA-RNA hybridization competition experiments by *Thomas*[8a] and *Conaughy* and *McCarthy*[8b], and a quantitative characterization of specificity in interactions between biological macromolecules has been presented by the author[9].

This report is intended as a general survey of the specific interaction problem. Quantitative data concerning specificity, as well as the relation of specificity to structural requirements and molecular size, will be discussed. Moreover, an attempt will be made to test some of the relations obtained for various chemical and molecular biology processes, and the possibility of predicting structures of compounds having a certain type of biological activity will also be considered.

2. Quantitative Characterization of Interaction Specificity

The requirements placed on a recognition process may be stated as follows[9a, 9b]: The "recognizer" A_0 should be able to complex with or precipitate only a certain molecular species B_0, *i. e.* the "correct" effector, out of N species $B_0, B_1, \ldots, B_{N-1}$ present in various concentrations. Also, the probability of all false recognitions should not exceed a threshold p_f. The degree of specificity of the recognition process may thus be

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characterized by the number N of possible effectors, among which A_0 recognizes the correct one, and the probability p_f of false recognitions.

Suppose that "recognition" consists in formation of a 1:1 complex from A_0 and B_0 in a simple chemical equilibrium reaction. This may be the case in cation binding by complexons like EDTA, or in enzymatic reactions in which an enzyme (A_0)-substrate (B_0) activated complex is formed (in the sense of absolute reaction rate theory). The reactions and equilibria for this case are

$$A_0 + B_i \rightleftarrows A_0B_i;$$

$$\frac{[A_0B_i]}{[A_0][B_i]} = K_{0i} \equiv e^{-\frac{G_{0i}}{RT}}; \qquad i = 0,1,\ldots,N-1 \tag{1}$$

The probability p_f of false recognition will be equal to the quotient

$$p_f = \frac{\sum_{i=1}^{N-1}[A_0B_i]}{[A_0B_0] + \sum_{i=1}^{N-1}[A_0B_i]} \approx \frac{\sum_{i=1}^{N-1}[B_i]K_{0i}}{[B_0]K_{00} + \sum_{i=1}^{N-1}[B_i]K_{0i}} \tag{2}$$

If the concentrations of all molecules B_i are appreciably higher than that of the "recognizer" A_0, the quantities of B_i bound in A_0B_i complexes will be negligible, even for B_0, and the B_i concentrations of eq. (2) are practically equal to the total B_i concentration. The specificity of the recognition process will be the higher the greater the quotients K_{00}/K_{0i} of the binding constants for the correct and false partners respectively, *i. e.* the higher the difference

$$\Delta G_i \equiv G_{0i} - G_{00} \tag{3}$$

between the affinity $-G_{00}$ of A_0 for the correct partner B_0 and those for the false ones $-G_{0i}$.

The precision of such a recognition process will decrease, *i. e.* p_f increase, if the total amount of B_i (and especially B_0) is comparable with or smaller than the quantity of the recognizer A_0[10]. In the extreme case when the quantity of A_0 surpasses the sum of quantities of B_i and all binding constants K_{0i} are great enough, practically the whole B_i quantities will be bound in A_0B_i complexes and the error probability p_f will reach a value of about 1.

The A_0-B_i interactions may have cooperative character. In the extreme case recognition implies precipitation of A_0 only by B_0, as in that of cation precipitation by a specific reagent or in antigen-antibody precipitation. For the simple case of 1:1 stoichiometry the solubility product relations required for correct recognition will be:

$$[A_0][B_0] \geq P_{00} \equiv e^{\frac{G_{00}}{RT}} \tag{4a}$$

$$[A_0][B_i] < P_{0i} \equiv e^{\frac{G_{0i}}{RT}}; \qquad i = 1,2,\ldots,N-1 \tag{4b}$$

If coprecipitation is neglected, the error probability p_f will be zero in this case.

The A_0B_i complexes may certainly also have more complicated stoichiometries, but it is unlikely that this will lead to any essential changes in the results of eq. (2) and (4).

A highly specific recognition thus requires a sufficiently high difference ΔG_i between the affinity G_{00} of A_0 for the correct B_0 effector and the affinity G_{0i} for false ones, as well as a sufficient excess of B_0 over A_0. With sufficiently high affinity differences ΔG_i the recognizer A_0 must be able to discern one effector, *i. e.* B_0, from N other effectors B_i. Small structural differences on the B_i regions which come into contact with A_0 will usually lead to only small affinity differences ΔG_i. Therefore the contact region between A_0 and the effectors B_i must be large enough to yield sufficiently large affinity differences ΔG_i for all the N different contact regions on the false effectors B_i.

Let us term these contact regions on A_0 and B_i "recognition sites". One can now understand why a high specificity—large values of N and ΔG_i (possibly as result of unfavorable B_i concentrations) and a small p_f—require large recognition sites. If the A_0 recognition site is to be left unchanged by the interactions with the different molecules B_i, a supplementary part of the A_0 molecule will be required to rigidize the recognition site. The molecule of A_0 must therefore consist of more than just its recognition site.

The situations described above refer to selection (recognition) processes proceeding in a single step. If the selectivity (specificity) of the recognizing agent is low, the separation of a certain component (B_0) out of the mixture ($B_0, B_1, \ldots, B_N$) can be performed by several selection steps with different selecting (recognizing) agents. This is the way ore analysis is performed by the methods of classical analytical chemistry. *Scherer*[11] proposed a similar way—"cascade regulation"—as a hypothetical cell regulation mechanism: restriction of cell protein synthesis to only those coded by a few genes (for example hemoglobin in erythrocytes) may proceed first as a restriction of transcription by repressors, secondly as a restriction in the passage of messenger RNA through the nuclear membrane, and thirdly as a selection by ribosomes of only some of the messenger RNAs available in the cytoplasm.

3. Structure and Interaction Affinity

According to the "lock-and-key" theory, a high interaction affinity ($-G_{0i}$) should require a steric complementarity between a certain part of the recognizer (lock, A_0) and the recognized molecule (key, B_0) and also a complementarity in intermolecular forces between the atoms of A_0 and B_0 which come into direct contact. If recognition means not only complex formation but also reaction (catalysis, enzymatic reactions), *i. e.* G_{00} is the lowest free enthalpy of activation, the tendency of B_0 to react, *i. e.* its reactivity, should also be a determining factor. What importance attaches to reactivity, steric complementarity, and intermolecular force complementarity, and how can these three factors be characterized?

In the catalysis of inorganic reactions, reactivity is the determining factor. The "recognizer" is the catalyst—an ion or, for heterogeneous catalysis, a constellation of atoms on the microcrystalline surface that is not larger than the elementary cell[5]. Ionic precipitate and complex formation[12] implies rigid sites, partition between different solvents[13] non-rigid sites, but here also the sites and molecules implied are small. One should not expect a particularly large specificity for such cases.

We shall be concerned mainly with interactions involving biomacromolecules, where the most interesting specificity problems appear. This is the domain of the lock-and-key effect, with macromolecules having large and sufficiently rigid cavities requiring various complementarity effects.

3.1. Reactivity Parameters

Correlations between various reactivity parameters of substrate molecules (B_i) and enzymatic reaction rates have been studied by the HMO method since the early fifties[14, 15]. The action of drugs was related to various reactivity parameters, and especially electronic charge on various atoms, *via* a perturbation theory by *Cammarata*[16]. This theory assumes the formation of a drug-receptor complex as the determining step in the biological response to the drug. The biological activity, expressed as the logarithm of the rate constant ($\log k$), or of the concentration for semimaximal biological effect, correlates well ($r > 0.95$) with parameters such as π- or total electron charge order at certain atoms (q_i) *via* linear or quadratic equations, but the correlation is valid only in series of similar molecules that do not differ too widely with regard to steric and general chemical structure. As a typical example, the relative phosphorylation rate ($\log V$) of 15 substituted purine nucleosides catalyzed by adenosine kinase correlates satisfactorily ($r = 0.9$) with the frontier electron density f_3^e at the N^3 atom of the base moiety, as calculated by the semiempirical SCF-MO method of *Pariser* and *Parr*. The correlation equation given by *Kaneti*[17] is

$$\log V = -23.9 f_3^e + 2.1; \quad \text{for adenosine, } V = 1 \qquad (5)$$

These 15 purine nucleosides have various substituents in the 1, 2, and 6 positions or some CH groups of the cycle substituted by N atoms. The $\log V - f_3^e$ correlation disappears if substitutions are performed in the sugar moiety (which do not affect f_3^e). Thus adenosine arabinoside or 2'-deoxyadenosine are phosphorylated very slowly ($V = 0.0$—-0.09), as are adenosines with large substituents on C-2 ($V = 0.0$ for CH_3, CH_3O, $(CH_3)_2N$, Cl, Br; however, the correlation applies for F and NH_2). This accords with the assumption that purine moiety is involved in binding of the ribosides to adenosine kinase by chelation[17].

3.2. Steric Fit

The importance of steric fit as compared to the chemical nature of the reacting groups follows from the fact that the reactions of similar substrates of the same chirality are also catalyzed, albeit at different rates. However, the enantiomers do not usually react at all, not even that of the most active substrate. In antigen-antibody interactions, polypeptide antigenic determinants have more "conformational" than "sequential" character, as remarked by *Sela*[18].

One could try to use *Taft*'s[19] steric constants E_s to characterize steric fit, but they reflect only a general screening effect of various substituents on a reaction center in a micromolecular reaction. An attempt by *Dupaix*, *Bechet*, and *Roucous*[20] to correlate α-chymotrypsin-catalyzed hydrolysis rates of acyl substituted *p*-nitrophenyl amino acid esters succeeded only for 9 compounds out of a series of 42 studied.

To correlate dissimilarities in steric fit with binding affinity decrease one should have a measure for these steric dissimilarities. However, no well established method seems to exist for this purpose. One could adopt the procedure used by *Rao* and *Rossmann*[21] in comparing suprasecondary structures in proteins: the two similar structures are superposed by a geometric technique so as to minimize the sum of the squares of the distances between all atoms assumed to be equivalent. This sum is then a measure for steric dissimilarity.

A more direct, although more approximative method is that of minimal steric differences (MSDs) of *Simon* and *Szabadai*[22]. The method consists in superposing the two molecules to be compared within limits allowed by bond lengths, bond angles, and free rotations (degrees of allowed variations: ≈ 0.2 Å for bond lengths; $\approx 20°$ for bond angles) and to count the second row atoms which do not superpose. Hydrogen atoms are hereby neglected. This MSD method was used in attempts to correlate the α-chymotrypsin hydrolysis rates of *N*-acetyl amino acid methyl esters listed by *Knowles*[23] and the decrease in biological activity produced by amino acid substitutions in hormonal oligopeptides (data listed in ref.[22]; 92 points). All MSDs were calculated relative to the hypothetical standard molecule *(6)* (Fig. 2). A satisfactory correlation was obtained for the α-chymotrypsin hydrolysis rates ($r = 0.93$) where correlation with Tanford hydrophobicities (HP)[24] of the amino acid side chains R is also obtained ($r = 0.80$; see Table 1). The best correlation equations are:

$$\log V = 0.70\,\text{MSD} + 2.10; \quad s = 0.82,\ r = 0.93,\ n = 14^{[*]} \qquad (6a)$$

$$\log V = 1.57\,\text{HP} - 6.3; \quad s = 1.35,\ r = 0.80,\ n = 14 \qquad (6b)$$

For 92 substituted oligopeptides, the correlation of biological activity *vs.* MSD (with respect to the unmodified oligopeptide) yielded $r = 0.55$. A mean affinity decrease of about 0.5 kcal per second row atom can be inferred[22].

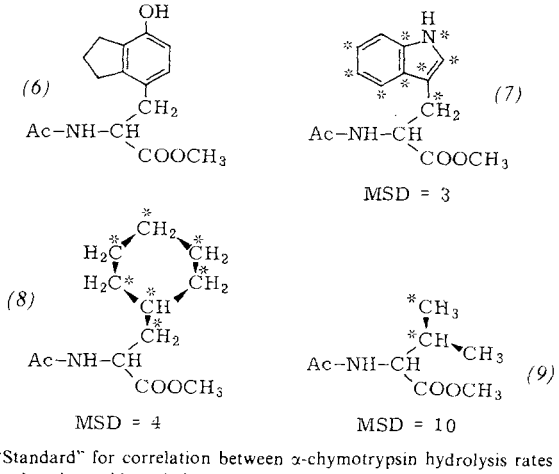


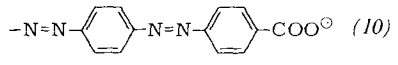
Fig. 2. "Standard" for correlation between α-chymotrypsin hydrolysis rates of *N*-acetyl amino acid methyl esters and minimal steric difference (MSD) of these molecules, and examples of MSD calculations. Hypothetical standard molecule *(6)*. Tryptophan side chain, *(7)*, MSD = 3. The difference between superposed pentacycles and hexacycles is taken as 1. The OH group of the standard is superposed on neither group of the tryptophan side chain. Cyclohexylalanine side chain, *(8)*, MSD = 4. The MSD is given by three atoms of the pentacycle and the OH group of the standard. Valine side chain, *(9)*, MSD = 10. Only two atoms are superposable on the standard. The atoms marked by an asterisk in *(7)*, *(8)*, and *(9)* are assumed to be superposable on atoms or groups of the standard *(6)*.

[*] s = standard deviation, r = correlation coefficient, n = number of derivatives.

Table 1. Kinetic parameters for the hydrolysis of *N*-acetyl amino acid methyl esters by α-chymotrypsin. V = second order rate constant at low substrate concentration; MSD = minimal steric difference; HP = Tanford hydrophobicity (ΔG_i for transfer of an amino acid side chain from water to *n*-octanol). For explanations see text.

$H_2NCHRCOOH$ in $AcNHCHRCOOCH_3$	log V	MSD	HP [kcal]
Trp	0.00	3	3.00
Tyr	−0.07	3	2.97
Cyclohexyl-Ala	−0.71	4	4.0
Phe	−1.00	4	2.65
α-NH_2-Heptanoic acid	−1.71	6	3.1
Met	−2.25	7.5	1.3
α-NH_2-Octanoic acid	−2.28	5	3.8
Leu	−2.43	7	2.49
Nor-Leu	−2.50	7	2.5
Nor-Val	−3.21	8	1.7
α-NH_2-Butyric acid	−4.35	9	1.1
Ala	−5.35	10	0.73
Val	−5.50	10	1.69
Gly	−8.65	11	0

The sparse success of biological activity—MSD correlations indicates that steric fit (complementarity) alone is insufficient for a high interaction affinity. Moreover, it is not the whole biologically active molecule that enters the "lock": the affinity of the antibody elicited by protein-bound *p*-(*p'*-azophenylazo)-benzoate towards benzoate ions substituted in different posi-



(10)

tions indicates a stringent steric fit requirement for the benzoate benzene ring (affinity increases of about 1.0 kcal/mol for *para* substitutions), but much looser steric requirements for the second benzene ring and for the second azo group (ref.[14], pp. 56—61). Thus it would appear that only the *p*-azobenzoate moiety of the antigen enters a "lock" in the elicited antibody.

3.3. Intermolecular Forces

Most reactions in the living cell take place in aqueous solution at a pH of about 7 and temperatures of about 30 °C. The formation of an A_0B_i complex often involves the passage of B_i from water to a more hydrophobic medium. One may thus expect to find correlations between biological activity of B_i and its hydrophobicity π_i, defined as:

$$\pi_i \equiv \log P_{i,\,oct} \tag{7a}$$

where $P_{i,oct}$ the partition coefficient of substance between a hydrophobic solvent (usually octanol) and water. Some ΔG_i values given by *Tanford*[24] are listed in Table 1 under the heading HP.

The use of the hydrophobicity constants π_i is demonstrated by the possibility of calculating the partition coefficient between a given solvent and water, $P_{i,solv}$, by means of two linear equations of the type:

$$\log P_{i,\,solv} = a_{solv} \log P_{i,\,oct} + b_{solv} \tag{7b}$$

One such equation is employed for solutes with a marked hydrogen donor character, and another for solutes with hydrogen acceptor character[13]. For example, partition coefficients for H donors and H acceptors in benzene can be calculated by means of eq. (7c) and (7d), respectively[25]:

$$\log P_{i,\,bz} = 1.019 \log P_{i,\,oct} - 1.401 \tag{7c}$$
$$n = 40,\ r = 0.948,\ s = 0.252$$

$$\log P_{i,\,bz} = 1.441 \log P_{i,\,oct} - 0.794 \tag{7d}$$
$$n = 20,\ r = 0.966,\ s = 0.254$$

These equations have been tested for large numbers n of solutes and give good correlation coefficients r. The hydrophobicity of a given molecule can be calculated from the hydrophobicities π_X of the groups of atoms which comprise the molecule and some increments for branching, ring closure, conjugation, *etc.*[13]. The hydrophobicity of a group X can be evaluated from the differences between partition constants of RX substitution derivatives and those of the unsubstituted parent molecule RH:

$$\pi_X = \log P_{RX,\,oct} - \log P_{RH,\,oct} \tag{7e}$$

Hydrophobicity constants were used especially by *Hansch et al.* for structure-activity correlations in the extrathermodynamic model[26a]. For example the inhibition of adenosine deaminase by various 9-benzyladenines can be described by:

$$-\log I_i = 0.453\,\pi_i - 1.194;\quad n = 8,\ r = 0.992 \tag{8a}$$

(I = inhibition constant)[26b], and the inhibition of the Hill reaction by *N*-phenylethyl carbamates by:

$$-\log C_i = 0.967\,\pi_i + 3.318;\quad n = 7,\ r = 0.982 \tag{8b}$$

(C = concentrations which give 50% inhibition)[26c]. Terms in π^2, σ^2 (Hammett constants), or reactivity indices should be also taken into account for some cases, according to the extrathermodynamic model. As example, for malate dehydrogenase inhibition by phenols (*meta* derivates are not included)[26d]:

$$-\log I_i = 0.73\,\sigma_i^2 - 0.65\,\sigma_i - 0.77\,\pi_i^2 + 2.44\,\pi_i + 3.47; \tag{8c}$$
$$r = 0.952$$

The correlational equations of *Hansch*[26] as well as those of *Cammarata* are valid only for classes of compounds with similar structure. This is not surprising since the configuration of the molecules, and hence the possibility of a steric fit into a "lock", is not accounted for by the reactivity parameters or by the hydrophobicity constants. One may nevertheless ask if a more complete consideration of intermolecular forces would not lead to correlation equations valid for compounds with a more extended domain of structural variation. Thus, the free energy required to transfer phenylalanine (side chain $-CH_2C_6H_5$) from aromatic solvents to water is + 1.8 kcal/mol (for equal concentrations), while for the same transfer from aliphatic solvents the corresponding value is only +0.3 kcal/mol[27]: aromatic rings should prefer aromatic to aliphatic environments. This preference is partly a steric effect—stacking of planar aromatic rings— and partly due to large perpendicular polarizabilities of aromatic rings; the van der Waals interaction energy is proportional to the product of the two polarizabilities.

We proposed a system of six types of intermolecular forces to characterize amino acid side chains[28a, 28b]: 1, hydrophobicity (HP, Tanford values); 2, special aromatic character (AR,

for Phe and Tyr 1.5 kcal/mol, as cited by *Némethy*[27] for the difference between aromatic-aromatic and aromatic-aliphatic interactions, 2.5 for Trp, 1.0 kcal/mol for His); 3, hydrogen bonding character, proton donor (HBD) or proton acceptor (HBA); 4, electrostatic charge at pH 7 (EC^+, EC^-); 5, electron accepting (ACT) or donating character (DCT) in charge transfer complexes (only Trp has donor character, the others are not active in charge transfer); 6, marked dipole moment not due to hydrogen bonds, directed towards the peptide backbone or the other end of the residue (μ^+, μ^- as an approximative characterization of uneven charge distribution, for Trp and Tyr).

These types of intermolecular forces were used in an attempt to correlate the relative decrease in biological activity produced in oligopeptides (antigenic determinants, hormones; most data taken from *Sneath*[29]) by amino acid substitutions with the sums of changes ΔHP, ΔAR, *etc.* in these types of intermolecular forces by the amino acid substitutions. The relative (as compared to the standard oligopeptides) decreased biological activity A, is given by following linear optimized equation[28b]:

$$-\log A_{calc} = 0.45 + 0.12\,\Delta HP + 0.69\,\Delta AR + 0.35\,\Delta HB + 0.004\,\Delta EC + 1.1\,\Delta DCT + 0.77\,\Delta\mu \quad (9)$$

$n = 92,\ r = 0.75,\ s = 0.84$

$-\log A_{exp}$ ranges from 0.00 to 4.65. The partial correlation coefficients for each of the six types of intermolecular forces are respectively 0.26, 0.53, 0.42, 0.22, 0.25, and 0.48, all being above the 95 % confidence limit. The linear correlation coefficient r is small, but the equation is valid for a large number n of substituted oligopeptides. All acceptor sites are proteins. Taking into account the widely varying decreases in activity produced by the same substitution at different positions in the peptide chain of the standard oligopeptide or in other standard compounds, this equation may be one of the best available to describe the effect of amino acid substitutions on oligopeptide-protein interactions, without considering interactions between amino acids on the peptide chain. The importance of the aromatic character (AR) and of the charge transfer interactions (DCT) is remarkable, as is the practically zero coefficient for changes in the electrostatic charge of the oligopeptide; possibly the charged groups of the oligopeptides are always directed towards the aqueous medium, even in complexes with proteins. Table 2 lists calculated [according to eq. (9)] and experimental $\log A$ values for derivatives of oxytocin substituted in positions 3, 4, and 8 (experimental data taken from *Sneath*[29]).

These types of intermolecular forces were adapted for an attempt to correlate the toxicity for mice and rats (molar LD_{50} values) with structure for organophosphorus compounds of the Schrader type[30a, 30b] $R^1R^2P(O)OR^3$. R^3 is here the most acidic group which is eliminated when the compound phosphorylates the acetylcholinesterase (the probable mechanism of action of these compound)[30c]. Modified Hammett constants σ of the substituents R^1, R^2, R^3 were also used in correlation. The optimized equation [similar to eq. (9)]—eight adjustable parameters, 71 compounds—yields a linear correlation coefficient $r = 0.70$. The coefficients for the hydrophobic, aromatic, and hydrogen bond parameters are similar to those of eq. (9) in absolute magnitude. The r value obtained here is also low, but the equation encompasses a wide range of different chemical structures (*i.e.* the substituents R^1, R^2, R^3) much broader than the range for which correlation equations of the type used by *Cammarata* and *Hansch* are valid.

Table 2. Experimental and calculated values, $\log A_{exp}$ [29] and $\log A_{calc}$ respectively, for the reduced biological activity A of oxytocins having substituted amino acid residues as compared with that of oxytocin itself; experiments on rats. $r = 0.95$, $n = 21$, $s = 0.62$.

Oxytocin: Cys-Tyr-Ile[3]-Gln[4]-Asn-Cys-Pro-Leu[8]-Gly

Substitution	$\log A_{exp}$	$\log A_{calc}$
Phe^3	1.25	1.51
Tyr^3	3.65	2.59
Trp^3	4.05	4.37
Leu^3	1.0	0.52
Val^3	0.9	0.60
Ser^4	0.3	0.64
Ala^4	1.1	1.25
AsN^4	0.6	0.46
Ile^8	0.2	0.52
Val^8	0.35	0.54
Lys^8	0.75	1.00
Arg^8	0.75	1.09
Phe^3Lys^8	1.95	2.06
Phe^3Arg^8	0.8	2.15
Phe^3His^8	2.4	2.79
Tyr^3Lys^8	4.6	3.14
Trp^3Lys^8	5.0	3.92
Ser^4Ile^8	0.5	0.71
$Phe^3AsN^4Lys^8$	2.2	2.07
$Phe^3Ala^4Lys^8$	2.95	2.86
$Phe^3Ser^4Lys^8$	2.7	2.25

3.4. Molecular Size

As mentioned in Section 1, a certain relation should exist between specificity and molecular size. A procedure will now be outlined for evaluation of the size of the recognition site (contact site between A_0 and the effectors B_i) required for a certain degree of specificity. The "recognizer" A_0 will be larger than the recognition site itself in order to ensure a certain rigidity of this site and possibly to allow for functions other than recognition *per se* (for example complement binding by antibodies).

The simplest reasoning is that adopted by *Thomas*[8a] and *McCarthy*[8b] in discussing the minimum number n of nucleosides in RNA oligonucleotides which can be recognized by absorbed DNA (viral, bacterial *etc.*) as self or alien in hybridization-competition experiments. These oligonucleotides are recognized by complementary base pair formation with DNA segments. If the DNA has N nucleotides there are also (approximately) N overlapping oligonucleotidic sequences on this DNA; if their primary sequences have a sufficiently random distribution, too short oligonucleotides of RNA coded by alien DNA may by chance have a sequence complementary to one on the absorbed DNA. If this is not to happen, n should be so large that the number 4^n of possible "words" in an "alphabet" of $\alpha = 4$ letters should be much higher than N. Thus:

$$\alpha^n \gg N;\quad n > \frac{\lg N}{\lg \alpha} \quad (10)$$

It is important that a "word" having a single changed "letter" as compared to the correct "word" (*i.e.* B_0) may be recognized by A_0, especially if the concentration of B_0 is low and that

of several false effectors B_i high. A highly simplified model for evaluating n in the general case by means of eqs. (2) or (4) is based on the following assumptions[9]:

i) All recognition sites of the effectors B_i have the same number n of monomeric units or atoms;

ii) The decrease in affinity ΔG_i (on going from A_0B_0 to A_0B_i) is proportional to the number ν_i of modifications by which the B_i recognition site differs from that on B_0 (Δg is the mean decrease per modification):

$$\Delta G_i = \nu_i \Delta g \tag{11}$$

iii) The false effectors B_i differ from B_0 by the same number ν of modifications within the combining site.

We must remember that N is the number of B_i types, which are all supposed to have different recognition sites, and α is the number of monomer units (or atoms) from which the B_i molecules are formed.

Going back to eqs. (2) and (1), with $\Delta G_i = G_{0i} - G_{00} = \nu \Delta g$ and $p_f \ll 1$:

$$p_f \cong \sum_{i=1}^{N-1} \frac{[B_i]K_{0i}}{[B_0]K_{00}} = \frac{\sum_1^{N-1}[B_i]}{[B_0]} e^{\frac{\bar{\nu}\Delta g}{RT}}; \quad \bar{\nu} = \frac{2.3RT}{\Delta g} \log \frac{[B_{tot}]}{p_f[B_0]} \tag{12}$$

In order that there are no accidental "false" recognitions a sufficiently low value must be obtained for the probability that the recognition site of any of the N false effectors B_i should differ by less than ν substitutions from that of B_0. Probability and combinatorial calculation techniques yield:

$$N C_n^{n-\nu+1} \cdot \alpha^{-(n-\bar{\nu}+1)} \ll 1 \tag{13}$$

which for $\nu = 1$ is identical with relation (10). Further calculations and use of the Stirling approximation for $x!$ furnishes the approximative result (see ref.[31], for $\log(ne/\nu - 1) \approx 1$):

$$n \gtrsim \bar{\nu} - 1 + \frac{(\bar{\nu}-1) + \log N}{\log \alpha} \tag{14}$$

If recognition leads to precipitation, and not to complex formation, the same results are valid, but the (mean) number ν of substitutions by which the false effectors B_i must differ from B_0 is to be calculated from eq. (15):

$$\bar{\nu} = \frac{2.3RT}{\Delta g} \log \frac{[B_{mx}]}{[B_0]} \tag{15}$$

with B_{mx} as the highest concentration of B_i which should be discerned (not precipitated) by A_0 from B_0.

4. Specificity in Some Chemical and Biochemical Processes

4.1. Antibody Elicitation by Nonself Antigens

The specificity of this process was analyzed on the basis of the assumption that elicitation of (primary) antibody production is triggered by precipitation of the foreign antigen (B_0) on the antibody combining sites (A_0) found on the surface of the respective immunocyte; "self" antigenic determinants (B_i) should thus not precipitate on these "self" antibody combining sites[31].

The lowest concentrations of foreign antigens ($[B_0]$ of eq. (15)) eliciting a primary response are about 10^{-6} mol/l for "weak" antigens and even 10^{-10} mol/l for "strong" ones. The maximal concentration of "self" antigenic determinants $[B_{mx}]$ may be about 10^{-3} mol/l, corresponding to serum globulin concentrations (see ref.[31]). Most antigenic determinants are peptide sequences made of $\alpha = 20$ amino acids. One amino acid substitution in the peptidic antigen produces a mean affinity decrease $\Delta g = 2.0$ kcal/mol. Equation (15) yields $\nu \approx 2$–5 for the concentration range between weak and strong antigens. The maximum possible number of "self" antigenic determinants would be equal to the number of overlapping short peptide sequences on all the proteins which may be coded by the haploid mammalian genome, *i.e.* $N \approx 10^9$; the real number may be perhaps $N \approx 10^7$, due to repetitions in the genome, nonavailability of some sequences, *etc.* For $N = 10^7$, $\alpha = 20$, $\nu = 2$–5, eq. (14) yields a number of $n \gtrsim 9$–13 amino acid residues for antigenic determinants which must be "sensed" by the antibody combining sites. Most antibody combining sites seem to accommodate 6–12 amino acid residues[32]. The smallest antigenic determinant is trialanine attached to a carrier protein[32d]; however, contributions from a more distant part of the carrier protein (not directly bound to the trialanine) to the antigenic determinant cannot be ruled out.

If foreign nucleic acids are to be discerned from endogenous ones containing only four monomeric units, the number of antigenic determinants should be approximately twice as large, *i.e.* $n \gtrsim 18$–25 monomeric units. Alternatively, the organism should not develop antibodies against nucleic acids made up of the usual four bases, which in fact seems to be the case.

Structure-affinity relationships concerning antibody eliciting haptens and similar molecules are discussed in great detail by *Pressman* and *Grossberg*[4]. The importance of conformation for antigen-antibody interaction was demonstrated by *Sela*[18]. Thus the α-helical polypeptide $(Tyr\text{-}Ala\text{-}Glu)_n$ elicits an antibody which gives no cross reaction with polylysine acylated at the ε-amino groups with the Tyr-Ala-Glu tripeptide

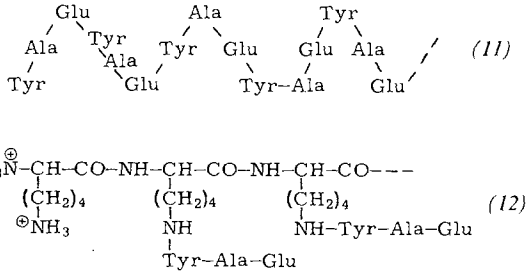
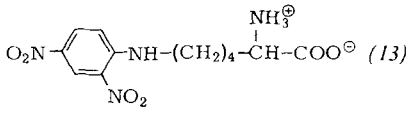


Fig. 3. α-Helical polypeptide $(Tyr\text{-}Ala\text{-}Glu)_n$ *(11)* and the antigen *(12)* obtained by coupling Tyr-Ala-Glu residues to ε-amino groups of poly-L-lysine (schematic).

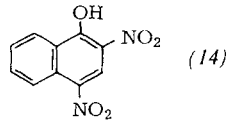
which is nonhelical under these conditions (Fig. 3). Reciprocal non-cross reactivity was also demonstrated. The oligopeptide $(Ala\text{-}Tyr\text{-}Glu)_n$ begins to react with the above mentioned anti-α-helical antibody at $n = 7$, although the peptide as such is not α-helical in solution. The antibody probably forces the antigen into an α-helical conformation[33a]. The reciprocal rela-

tion between the net charge of the immunogenic macromolecules and that of the elicited antibodies was also demonstrated by *Sela*[33b].

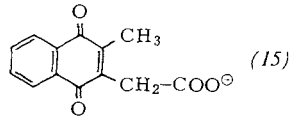
Completely synthetic antigens were also obtained[33c]. It appears that a minimum molecular weight is required for antigenicity: dinitrophenyl-(L-Lys)$_n$ becomes antigenic for guinea pigs only for $n \geq 7$.



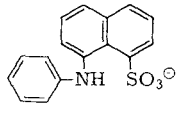
(13)



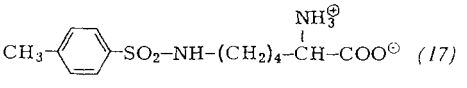
(14)



(15)



(16)



(17)

Fig. 4. Molecules which bind to the MOPC-460 myeloma protein: N^{ϵ}-(2,4-dinitrophenyl)lysine, *(13)*; 2,4-dinitronaphthol, *(14)*; Menadione, *(15)*. Molecules which do not bind to the protein: 8-anilino-1-naphthalenesulfonate, *(16)*; N^{ϵ}-(*p*-toluenesulfonyl)lysine, *(17)*.

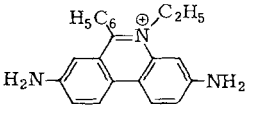
For oligopeptidic haptens and their derivatives obtained by amino acid substitutions, correlation of affinity decrease (towards the elicited antibody) with differences in intermolecular force parameters [in the sense of eq. (9)], yields a correlation coefficient $r \approx -0.75$[28]. An interesting example of specificity determined by intermolecular forces is provided by the affinity of the mouse myeloma proteins MOPC-460 and MOPC-315 for various small molecules (Fig. 4). The former protein strongly binds ($K \approx 10^{-4}$ mol/l) various aromatic nitro derivatives and quinones, *i.e.* molecules with an electron accepting character in charge transfer complexes (ACT); no detectable binding occurs with other aromatic molecules having similar steric structure but lacking this property (for example aromatic amines[34a-34c]). Spectral studies suggest that the combining sites of these immunoglobulins contain two tryptophan residues which form charge transfer complexes with aromatic nitro derivatives[34d].

4.2. Repressor-Operator Interactions

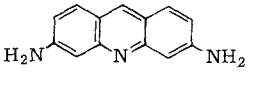
The best studied system in the field is the *Escherichia coli* lac operon. The repressor-operator binding is a simple association equilibrium with the dissociation constant $K \approx 10^{-13}$ mol/l[35a]. The *E. coli* chromosome consists of $N = 4.5 \times 10^6$ base pairs, or about the same number of short overlapping oligonucleotide sequences. An 300-fold excess of *E. coli* DNA without operator gene does not compete detectably with the operator for the repressor[35b], *i.e.* $p_f \approx 10^{-3}$. Point mutations in the lac operator decrease the affinity for the repressor by a factor of 8 to 1000[35d]. The mean affinity decrease per base pair substitution is thus $\Delta g \approx 2.0$ kcal/mol; from eq. (12) $\nabla \approx 7$. As there are $\alpha = 4$ types of base pairs, eq. (14) requires $n \gtrsim 27$ base pairs for the lac operator gene[36]. A calculation by *Sadler* and *Smith*[35e] based upon an assumed binomial distribution of oligonucleotides as compared to the operator segment gives $n = 18$ base pairs. According to an experimental study by *Gilbert* and *Maxam*[37], the lac operator gene comprises about 27 base pairs. *Maniatis* and *Ptashne*[38] indicate a length of about $n = 35$ base pairs for the λ-bacteriophage operator gene unit. Six such identical units are present in the complete operator gene, and the specificity requirements must be the same as for the lac repressor-operator system: the λ-bacteriophage repressor is coded by a permanent gene of the *E. coli* genome.

Binding of the *E. coli* lac repressor to the operator does not imply an unwinding of the DNA. Its dependence upon the ionic strength indicates an charge product of -6 electronic units for the interaction of the two partners[35c]. The primary structure of the lac operator gene, which was deciphered by *Sadler* and *Smith*[35] and by *Gilbert* and *Maxam*[37], presents some interesting symmetries. The primary structure of the lac repressor was also sequenced by *Müller-Hill et al.* and *Beyreuther et al.*[39]. A structural model was proposed for the specific interaction of the double helix DNA of the operator and the sequence of the amino end of the repressor, which presumably has an α-helical structure[39]. This space filling model is based on specific hydrogen bonds between amino acid residues and corresponding groups on the bases and phosphate groups in the deep groove of the DNA. However, according to *Weber et al.*[40], a mutated repressor, whose hydrogen bonding ability for the operator should be lowered according to the model, does not display a markedly decreased affinity.

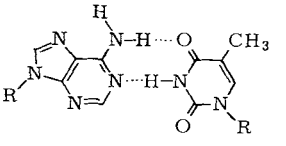
Aromatic molecules are intercalated fairly easily in the DNA double helix by stacking according to the principle of maximum overlap[41a]. Ethidium bromide or proflavin are readily incorporated into the DNA double helix with an uncoiling of only 12° per intercalation[41b] (Fig. 5). Polyadenine binds very readily to tryptophan which contains an aromatic ring of the same shape and size as purine, less so phenylalanine and histidine[41c]. Poly-dAT binds L-Lys-L-X—NH_2 dipeptides with increasing affinity in the series X = leucine < tyrosine < phenylalanine < tryptophan[41d]. Aromatic amino acid



(18)



(19)



(20)

Fig. 5. Ethidium ion *(18)* and proflavin *(19)* and their similarity to the AT base pair *(20)* in DNA.

residues of the repressor may be bonded by stacking in the operator DNA double helix and some preferences may appear due to reciprocal orientations of dipole moments of the aromatic amino acid rings and the neighboring nucleic acid bases[42].

4.3. Specificity in Reactions with Small Molecules

The case of inorganic analytical reagents has already been mentioned. A typical reagent for cations is ethylenediaminetetraacetic acid (EDTA, Fig. 1). It can specifically complex Ca^{2+} ions in a mixture of alkali metal and alkaline earth ions and is thus suitable for titrimetric determinations. The dissociation constant of $[CaEDTA]^{2-}$ is 2.58×10^{-11} mol/l, and that of $[MgEDTA]^{2-}$ 2.04×10^{-9} mol/l[13,43]; hence a hundredfold excess of Mg^{2+} ions must be present to compete successfully for this complexon. Compared with repressor-operator or antigen-antibody interactions, this specificity is low although sufficient for analytical chemistry.

The substrate specificity of catalytic reactions is also low compared with interactions between biological macromolecules. For example, the activation energies for dehydration of various alcohols over Al_2O_3 at 350 °C are 20.2, 18.3, and 16.4 kcal/mol for ethanol, 1-propanol, and isobutanol respectively[43]. The specificity of a catalyst may be higher: the relative rates of hydrogenation of the ethylenic double bond over Rh, Pd, Pt, and Fe catalysts are approximately 1000:100:10:1 although the interatomic distances increase by less than 0.1 Å in this series of catalysts[43].

The structural features bearing upon substrate-inhibitor-enzyme interactions in enzymatic reactions have been discussed at length by *Webb*[44]. We shall first consider the binding affinity to the catalytic site of the enzyme and the transformation rate of the bound molecule. Molecules exhibiting high affinity and low transformation rate will be competitive inhibitors. In enzymatic elimination of the *p*-nitrophenyl group from the series of amino acid derivatives

$$C_6H_5{-}CH_2{-}O{-}CO{-}NH{-}CHR{-}CO{-}O{-}C_6H_4{-}NO_2$$

by hydrolysis with chymotrypsin, the D-phenylalanine derivative has the highest binding constant ($K = 3.8 \times 10^{-7}$ mol/l; L-Phe derivative $K = 4.5 \times 10^{-7}$ mol/l), the L-phenylalanine derivative the highest transformation rate ($k_3 = 39\,s^{-1}$; D-Phe derivative $k_3 = 0.18\,s^{-1}$). The second order rates V at low substrate concentration are 8.1×10^6 l mol^{-1} s^{-1} for the L-derivative and only 4.8×10^4 l mol^{-1} s^{-1} for the D derivative. Some other L amino acid derivatives give $V = 3.5 \times 10^6$ for the Trp derivative, 2.5×10^4 for the Asn derivative, and 3.1×10^4 l mol^{-1} s^{-1} for the norvaline derivative[20].

The specificity of enzymatic reactions is also low in comparison with the interactions between macromolecules. Thus iodoacetate (ICH_2COO^-), considered as a specific inhibitor of glyceraldehyde dehydrogenase, also inhibits at least 55 other enzymes and a 10^{-3} M concentration of trivalent arsenic compounds—specific inhibitors of keto acid oxidation—also inhibits another 52 enzymes[44]. The specificity requirements placed upon enzymatic reactions within the cell are likewise much lower than those found for antigen-antibody or repressor-operator interactions: the number of small molecules within the cell from which an enzyme must recognize the correct partner is certainly not higher than $n = 10^3$, while an error threshold $p_f = 0.01$ is probably also sufficient[9c].

A very low error threshold is required in DNA replication: the frequency of point mutations (false base incorporation) is 10^{-8}—10^{-11} per base pair and replication[45]; but the DNA-replicase system only has to discern the correct partner among the $N = 4$ deoxyribonucleotides available. The replicase system can be easy "tricked" by base analogs as bromouridine or azaguanine, which are incorporated with high frequency in replicating DNA. According to eq. (12), an error threshold $p_f = 10^{-8}$—10^{-11} and $N = 4$ requires an affinity difference of $\Delta G \approx 11$—16 kcal/mol, which cannot be explained solely by differences in complementary hydrogen bonding in base pairs. A hypothetical explanation for the high precision of replication was proposed by *Kubitscheck* and *Henderson*[46]: the molecular region implied in recognition is larger than the complementary hydrogen bond forming groups of the base pair. The replicase should also sense the groups in positions 5 and 6 of pyrimidine and 6 and 7 of purine.

5. Conclusions. Forecasting of Structures with Particular Biological Activity

The search for substances possessing a desired biological activity is as old as medicine itself. The extensive systematic work performed in our century has been very successful although the theoretical basis may have been rather sparse. *Ehrlich*'s Salvarsan (Fig. 1) was the result of a search on several hundred substances; the idea was probably based on the observation of specific staining of bacteria by certain azo dyes and that the introduction of arsenic renders substances toxic (for other examples see ref.[47]).

Examples may also be given of very extensive but not very successful searches, *e.g.* the testing of the perhaps hundreds of thousands of compounds listed in "Cancer Screening Data", and the not very impressive results of cancer chemotherapy. Principles for guiding such research, even if only of probabilistic value, are thus badly needed. The studies by *Cammarata*[16] and *Hansch*[26] already mentioned are on these lines.

A principle which does not seem to be very widely recognized is the need for a minimum molecular size for a high specificity. Drugs such as sulfonamides block some enzymes of bacteria which differ significantly from their mammalian counterparts; even if these drugs combine with several proteins of the mammalian cell, this may have no dramatic biologic effect. Cancer—as suggested especially by the viral theories—resides in some defect within the genome, perhaps in some viral oncogens incorporated in the host genome. Drugs against various cancers should thus have a specificity comparable with the repressor proteins[48], and it is rather hopeless to search for some simple molecule which could adequately fulfill this task. With macromolecules, the number of possible combinations reaches astronomical figures and it will certainly be very difficult to develop a strategy for search in this case. Problems of strategy also appear in searches for structures with a given biological activity in the area of antibacterial drugs, pesticides, plant growth stimulators, *etc.* Equations of the type (5)—(9) may indicate, for the given class of compounds, what sort of substitution (hydrophobic groups, electron attracting groups, *etc.*) favors the desired type of biological activity. If second power terms are included, one can also indicate optimal values for the corresponding structural parameters (optimal hydrophobicity, optimal electronegativity, *etc.*).

Another search strategy is based on the *Free* and *Wilson* model[49]. In this model, the biological activity is considered as the sum of contributions from molecular segments which may contain different substituents. Taking a certain minimum number of biological activities, the effects of the substituents in the different segments are calculated and one can predict, within the given set of segments and substituents, which molecule should be the most active.

Several classes of desired biological effects can be achieved with a large number of compounds which often vary considerably in their chemical structure. The amount of calculation involved in using such large series of data in forecasting the optimal chemical structure may impose computerization. Pertinent search strategies recently proposed by *Hiller et al.*[50] are based either on a perceptronic, a logico-structural, or a topographic algorithm. Some tests on different sets of chemical compounds give an average reliability of 75—80% in predicting active and non-active compounds, respectively. One problem of such computerized search methods is that of finding an adequate "catalog" of structural parameters for characterizing the compounds.

At present the methods of forecasting structures with a desired biological activity give satisfactory results only within classes of compounds possessing similar chemical structures. The high requirements of specificity in certain cases impose the use of molecules of increasing size and complexity, as illustrated by the last decade's antibiotics. This leads to an enormous increase in the number of compounds be tested; their synthesis would also be extemely time consuming. Hence more knowledge about structural parameters determining biological activity and specificity is badly needed.

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[1] *E. Fischer*, Chem. Ber. *27*, 2985 (1894).

[2] *P. Ehrlich:* Studies on Immunity. Wiley, New York 1906.

[3] *S. Arrhenius:* Immunochemistry. Macmillan, New York 1907.

[4] *D. Pressman* and *A. L. Grossberg:* The Structural Basis of Antibody Specificity. Benjamin, New York 1968.

[5] *A. A. Balandin:* Multipletnaia teoria kataliz (Multiplet Theory of Catalysis). M. G. U. Moscow 1963—1964.

[6] *A. D. Riggs, H. Suzuki,* and *A. Bourgeois,* J. Mol. Biol. *48*, 67 (1970).

[7] *M. V. Volkenshtein* and *A. M. Eliashevich,* Dokl. Akad. Nauk SSSR *136*, 1216 (1961).

[8] a) *C. A. Thomas, jr.,* Progr. Nucl. Acid Res. Mol. Biol. *5*, *315 (1966)*; b) *B. L. Conaughy* and *B. J. McCarthy,* Biochim. Biophys. Acta *149*, 180 (1967).

[9] a) *Z. Simon,* J. Theor. Biol. *9*, 414 (1965); b) Rev. Roum. Biochim. *9*, 337 (1972); c) Biochimie cuantică şi interacţii specifice (Quantum Biochemistry and Specific Interactions). Edit. Stiinţifică, Bucureşti 1973.

[10] *J. Ninio,* Progr. Nucl. Acid Res. Mol. Biol. *12*, 13 (1973).

[11] *K. Scherer,* Abh. Deut. Akad. Wiss. Berlin. Kl. Med. *1968*, 259.

[12] *G. Schwarzenbach,* Advan. Inorg. Chem. Radiochem. *7*, 251 (1961).

[13] *A. Leo, C. Hansch,* and *D. Elkins,* Chem. Rev. *71*, 525 (1971).

[14] *B. Pullman* and *A. Pullman:* Quantum Biochemistry. Wiley, New York 1963.

[15] *B. Pullman,* Advan. Quantum Chem. *4*, 267 (1968).

[16] *A. Cammarata* in *R. Kier* and *B. Lemont:* Molecular Orbital Studies. Chemical Pharmacology Symposium. Springer, New York 1970, p. 156, and other papers of this symposium.

[17] *J. Kaneti,* J. Theor. Biol. *38*, 169 (1973).

[18] *M. Sela,* Naturwissenschaften *56*, 206 (1969).

[19] *R. W. Taft, jr.* in *M. S. Newman:* Steric Effects in Organic Chemistry. Wiley, New York 1956, p. 586.

[20] *A. Dupaix, J. J. Bechet,* and *C. Roucous,* Biochemistry *12*, 2559, 2566 (1973).

[21] *S. T. Rao* and *M. G. Rossmann,* J. Mol. Biol. *76*, 241 (1973).

[22] *Z. Simon* and *Z. Szabadai,* Studia Biophys. (Berlin) *39*, 123 (1973).

[23] *J. R. Knowles,* J. Theor. Biol. *9*, 213 (1965).

[24] *C. Tanford,* J. Amer. Chem. Soc. *84*, 4240 (1962).

[25] *C. Hansch:* Pomona College Medicinal Chemistry Project. Claremont, Calif. 1973.

[26] a) *C. Hansch* and *T. Fujita,* J. Amer. Chem. Soc. *86*, 1616, 5175 (1964); b) *H. J. Schaffer, R. N. Johnson,* and *E. Oddin,* J. Med. Chem. *13*, 452 (1970); c) *C. Hansch* and *E. W. Deutsch,* Biochim. Biophys. Acta *112*, 381 (1966); d) *R. T. Wedding, C. Hansch,* and *T. R. Fukuto,* Arch. Biochim. Biophys. *121*, 9 (1967).

[27] *G. Némethy,* Angew. Chem. *79*, 260 (1967); Angew. Chem. internat. Edit. *6*, 195 (1967).

[28] a) *Z. Simon,* Rev. Roum. Biochim. *5*, 319 (1968); b) *Z. Szabadai* and *Z. Simon, ibid. 9*, 327 (1972); c) *Z. Simon, Z. Szabadai,* and *J. Miklos, ibid. 8*, *79 (1970)*.

[29] *P. H. A. Sneath,* J. Theor. Biol. *12*, 157 (1966).

[30] a) *R. Vîlceanu, A. Chiriac, Z. Szabadai,* and *Z. Simon:* Rev. Roum. Biochim. *10*, 239 (1973); b) in preparation; c) *R. D. O'Brien* in: Chimie Organique du Phosphore. Colloques Internationales CNRS. Editions CNRS, Paris 1970, p. 353.

[31] *Z. Simon* and *V. Ghetie,* Rev. Roum. Biochim. *8*, 261 (1971).

[32] a) *M. F. Burnet:* Cellular Immunology. Melbourne University Press, Melbourne 1969; b) *E. L. Kabat:* Structural Concepts in Immunology and Immunochemistry. Holt, Rinehart and Winston, New York 1968; c) *J. Fischer, J. Spragg, R. C. Talamo, J. V. Pierce, K. Suzuki, K. F. Austen,* and *E. Haber,* Biochemistry *8*, 3750 (1969); d) *J. Schaechter,* Nature *228*, 638 (1970).

[33] a) *M. Sela,* Ann. N. Y. Acad. Sci. *190*, 181 (1971); b) *J. B. Robbins, E. Mozes, A. Rimon,* and *M. Sela,* Nature *213*, 1013 (1967); c) *M. Sela,* Science *166*, 1365 (1969).

[34] a) *B. M. Jaffe, E. S. Simms,* and *H. N. Eisen,* Biochemistry *10*, 1963 (1971); b) *R. W. Rosenstein, R. A. Musson, M. Y. K. Armstrong, W. H. Königsberg,* and *F. F. Richards,* Proc. Nat. Acad. Sci. USA *69*, 877 (1972); c) *J. H. Rockey, P. C. Montgomery, B. J. Underdown,* and *K. J. Dorrington,* Biochemistry *11*, 3172 (1972); d) *J. Haimovich, H. N. Eisen, E. Hurwitz,* and *D. Givol, ibid. 11*, 2389 (1972).

[35] a) *A. D. Riggs, H. Suzuki,* and *S. Bourgeois,* J. Mol. Biol. *48*, 67 (1970); b) *A. D. Riggs, R. F. Newby,* and *S. Bourgeois, ibid. 51*, 303 (1970); c) *A. D. Riggs, S. Bourgeois,* and *M. Cohn, ibid. 53*, 401 (1970); d) *T. F. Smith* and *J. R. Sadler, ibid. 59*, 273 (1971); e) *J. R. Sadler* and *T. F. Smith, ibid. 62*, 139 (1971).

[36] *Z. Simon,* Studia Biophys. (Berlin) *26*, 179 (1971).

[37] *W. Gilbert* and *A. Maxam,* Proc. Nat. Acad. Sci. USA *70*, 3581 (1973).

[38] *T. Maniatis* and *M. Ptashne,* Proc. Nat. Acad. Sci. USA *70*, 1531 (1973).

[39] a) *K. Adler, K. Beyreuther, E. Fanning, N. Geissler, B. Gronenborn, A. Klemm, B. Müller-Hill, M. Pfahl,* and *A. Schmitz,* Nature *237*, 322 (1972); b) *K. Beyreuther, K. Adler, N. Geissler,* and *A. Klemm,* Proc. Nat. Acad. Sci. USA *70*, 3576 (1973).

[40] *K. Weber, T. Platt, D. Ganem,* and *J. H. Miller,* Proc. Nat. Acad. Sci. USA *69*, 3624 (1972).

[41] a) *A. M. Craig* and *I. Isenberg,* Proc. Nat. Acad. Sci. USA *67*, 1337 (1970); b) *W. Fuller* and *M. J. Warring,* Ber. Bunsenges. Phys. Chem. *68*, 805 (1971); c) *M. Raczka* and *M. Mandel,* Proc. Nat. Acad. Sci. USA *68*, 1190 (1971); d) *E. J. Gabay, K. Sanford, C. S. Baxter,* and *L. Kapecak,* Biochemistry *12*, 402 (1973).

[42] *Z. Simon,* Studia Biophys. (Berlin) *28*, 179 (1972).

[43] Spravochnik Chimika (Chemical Tables): Edit. Khimia, Moscow, 1965, Vol. 3, p. 162.

[44] *J. L. Webb:* Enzyme and Metabolic Inhibitors. Academic Press, New York 1963.

[45] *J. W. Drake,* Nature *221*, 1132 (1969).

[46] *H. E. Kubitscheck* and *T. R. Henderson,* Proc. Nat. Acad. Sci. USA *55*, 512 (1966).

[47] *A. Albert:* Selective Toxicity (Russian translation). Izd. Inostr. Lit. Moscow 1953.

[48] *Z. Simon, Rev. Roum. Biochim. 6*, 239 (1969).

[49] *S. M. Free* and *J. N. Wilson,* J. Med. Chem. *7*, 398 (1964).

[50] *S. A. Hiller, A. B. Glaz, V. E. Holender, L. A. Rastrighyn,* and *A. B. Rozenblat,* Khim. Farm. Zh. *11*, 18 (1972).

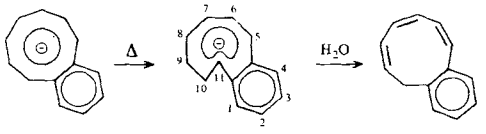
trans-Benzocyclononatetraenyl Anion[**]

By *A. G. Anastassiou* and *E. Reichmanis*[*]

The benzocyclononatetraenyl anion *(1)* was recently prepared in our laboratories and was shown to be strongly diatropic by NMR[1]. Despite its obvious aromatic character however, the molecule *(1)* is thermally labile, undergoing clean thermal isomerization on prolonged standing at ambient temperature. Presently, we should like to relate out experience along these lines.

On warming at 56 °C, in liquid ammonia, *(1)* undergoes clean unidirectional isomerization with $k=(2.56\pm0.22)\times10^{-5}\,s^{-1}$, ($\Delta G^{\neq}=26.2$ kcal/mol). The thermolysis product was securely characterized as *(2)* by careful analysis of its nuclear magnetic resonance spectrum[2] featuring, in particular, a high-field ($\tau=12.35$) strongly coupled ($J=16.0$ Hz) doublet. This key resonance unmistakably implicates the presence of a strongly shielded "inner" proton bound to a *trans* bond and located adjacent to the ring juncture. The remainder of the spectrum is also seen to be consistent with structure *(2)*. Specifically, we draw attention to the relatively small coupling constants associated with the C—H bond directly linked to the *trans* function, *i.e.*, $J_{9,10}=5.0$ Hz and $J_{9,8}=8.5$ Hz, which clearly reflect the regional reduction of effective ring size due to the presence of the *trans* bond. By contrast, *all* nonbenzylic protons in the spectrum of the all-*cis* counterpart *(1)* are associated with the same large coupling constant ($J=12$ Hz)[3] whose magnitude is clearly reflective of the wide frame angles expected of a planar all-*cis* nine-membered ring.

Chemically, the molecule was shown to be a benzocyclononatetraenyl anion through its conversion to 5*H*-benzocyclononatetraene *(3)* on exposure to moist ether. It is interesting to note in this connection that *(3)* is the only benzocyclononatetraene formed (>90%) from *(2)* irrespective of whether quenching was effected under conditions of thermodynamic or kinetic control. Very likely the high regioselectivity of this protonation results largely from the molecule's tendency to rid itself of the added strain introduced by the *trans* function.



(1) *(2)* *(3)*

The question now arises as to why the anion *(1)* undergoes *cis*→*trans* isomerization. At first glance, this transformation emerges as all the more puzzling in light of the well documented affinity of the parent, *i.e.*, the cyclononatetraenyl anion, to undergo the reverse process, *i.e.*, *trans*→*cis* isomerization, when warmed to ambient temperature[4]. Closer scrutiny does however reward one with a rational explanation for the *(1)* to *(2)* isomerization. Briefly, it is seen that *(1)*, unlike its parent, is plagued by a pair of *peri* H—H interactions about the juncture which ought to be quite severe for a molecule of its size[5] and thus potentially damaging to the preservation of planarity. Obviously, the molecule may relieve the steric congestion introduced by the *peri* interaction in one of two ways, (i) it may distort, thus *partially* relieving both sets of H—H repulsions and (ii) it may undergo *cis*→*trans* isomerization of a double bond carrying one of the *peri* hydrogens, thus *completely* removing one set of H—H repulsions while preserving the other. Not unexpectedly, the molecule shows preference for the second alternative since only in this manner is it able to preserve its planarity and thus its aromaticity.

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[1] *A. G. Anastassiou* and *R. C. Griffith*, J. Amer. Chem. Soc. 96, 611 (1974).

[2] The spectrum was recorded at 100 MHz in NH_3 at −25 °C. Trimethylamine was employed as internal standard. $\tau=1.85$ (m, 1 benzenoid H), 2.01 (m, 1 benzenoid H), 2.18 (dd, H^{10}, $J_{10,9}=5.0$ Hz, $J_{10,11}=16.0$ Hz), 2.7—3.1 (m, H^5, H^6, 2 benzenoid H), 3.12 (dd, H^8, $J_{8,7}=11.5$ Hz, $J_{8,9}=8.5$ Hz), 3.56 (dd, H^9, $J_{9,8}=8.5$ Hz, $J_{9,10}=5.0$ Hz), 3.75 (dd, H^7, $J_{7,6}=9.0$ Hz, $J_{7,8}=11.5$ Hz), 12.35 (d, H^{11}, $J_{11,10}=16.0$ Hz).

[3] These coupling constants were extracted from the spectrum determined at 220 MHz. We are indebted to Prof. *S. W. Staley* for this information.

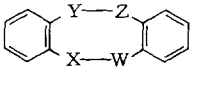
[4] *G. Boche, D. Martens*, and *W. Danzer*, Angew. Chem. *81*, 1003 (1969); Angew. Chem. internat. Edit. *8*, 984 (1969).

[5] The destabilizing interaction between vicinal protons of a planar nine-membered ring is expected to be significant: *H. E. Simmons* and *J. K. Williams*, J. Amer. Chem. Soc. *86*, 3222 (1964).

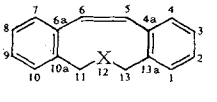
Conformational Studies on Aza and Thia Derivatives of 12,13-Dihydro-11*H*-dibenzo[*a*,*e*]cyclononene

By *W. David Ollis* and *J. Fraser Stoddart*[*]

The recognition[1,2] that many heterocyclic "6, 8, 6" systems *(1)* exist in solution in diastereomeric Chair[3] and Boat[3] conformations has encouraged us to examine related "6, 9, 6" systems *(2)*.



(1)



(2a), X = CH_2
(2b), X = NCH_3
(2c), X = $NCH_2C_6H_5$
(2d), X = S

The *N*-benzyl derivative 12-benzyl-12,13-dihydro-11*H*-12-azadibenzo[*a*,*e*]cyclononene *(2c)* (m.p. 109—111 °C) was prepared following the known route[4] to the *N*-methyl derivative *(2b)* using a Stevens rearrangement followed by a Hofmann elimination. The thia derivative *(2d)* (m.p. 101—103 °C) was synthesized by the sequence: (i) photochemical transformation of *trans*-2,2'-stilbenedimethanol[5] into the *cis*-isomer (m.p. 113—114 °C), (ii) conversion with PBr_3 into the *cis*-2,2'-bis(bromomethyl)stilbene (m.p. 125—127 °C), and (iii) ring closure with Na_2S—MeOH to *(2d)* (m.p. 101—103 °C).

The temperature-dependent ^{1}H-NMR spectra (Table 1) shown by the aza derivative *(2b)* are typical for this class of substances

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Table 1. ^{1}H-NMR spectral changes (100 MHz) and activation parameters for the conformational changes of the compounds *(2b)*—*(2d)* in $CDCl_3$.

Compound	Group	Temp. (°C)	Chemical shifts (τ) [a] Coupling constants [Hz]	Sites involved in exchange [a]	$\Delta G^{\neq}$ [kcal/mol]	Process	Relative Populations p_1	p_2
(2b)	*N*-methyl	−30	7.62 (A), 7.70 (B)					
		+68	7.64 (AB)	A→B	15.4	C→Boat	0.905	0.095
	11-CH_2, 13-CH_2	−30	5.82 (A1), 6.22 (B1), J = 13.9, 6.23 (AB2)					
		+30	5.86 (A12), 6.26 (B12), J = 13.9	A1→A2; B1→B2	15.9	C→Boat	0.905	0.095
		+68	6.12 (AB12)	A1⇌B1	16.3	C⇌C*		
(2c)	*N*-α-benzyl	−20	6.23 (A), 6.48 (B)					
		+45	6.28 (AB)	A→B	14.9	C→Boat	0.86	0.14
	11-CH_2, 13-CH_2	−20	5.84 (A12), 6.08 (B12), J = 13.9, 6.17 (AB2)	A1→A2; B1→B2	14.9	C→Boat	0.86	0.14
		+45	6.08 (AB12)	A1⇌B1	16.1	C⇌C*		
(2d)	11-CH_2, 13-CH_2	−10	5.93 (A1), 6.34 (B1), J = 14.2					
		+40	6.16 (AB1)	A1⇌B1	15.5	C⇌C*		

[a] Sites are designated (A) and (B) for uncoupled two-site systems; sites that represent two time-averaged signals are designated (AB). Sites are designated (A1), (B1), (A2), and (B2) for four-site systems where there is coupling in the form of two AB systems. Sites that represent two time-averaged signals are designated (AB1) [average of (A1) and (B1)] and (A12) [average of (A1) and (A2)] *etc.*

and demonstrate that two diastereomeric conformations are populated in solution. At low temperatures the 11-CH_2 and 13-CH_2 protons give (i) an AB system assignable to a relatively rigid conformation and (ii) a singlet associated with a rapidly inverting conformation. Increase in temperature results first of all in a coalescence of the AB system and the singlet followed by further coalescence finally yielding a sharp singlet. The two processes [*(2b)*, see Table 1; $\Delta G^{\neq}$ = 15.4—15.9, and 16.3 kcal/mol, respectively] have been subjected to line shape analysis[1].

Conformational analysis and strain energy calculations direct attention to five particular conformations: (1) A relatively rigid chair conformation [C, *(3)*, C_s symmetry], (2) a boat conformation [B, *(4)*, C_s symmetry], (3) a twist-boat conformation [TB, *(5)*, C_2 symmetry], (4) asymmetric distorted-boat conformation [DB, *(6)* and *(7)*], and (5) a transition state conformation [TS, *(8)*, C_s symmetry]. Strain energy calculations demonstrate that the C *(3)* and DB conformations [*(6)* and *(7)*] correspond to ground state conformations. The conformational itinerary associates the ground state conformations (C, DB1, DB2 and their enantiomeric or degenerate partners C*, DB1*, DB2*) with the transition states (B, TB, TS, and B*, TB*, TS*). This is the general situation for compounds *(2b)*—*(2d)* (Fig. 1).

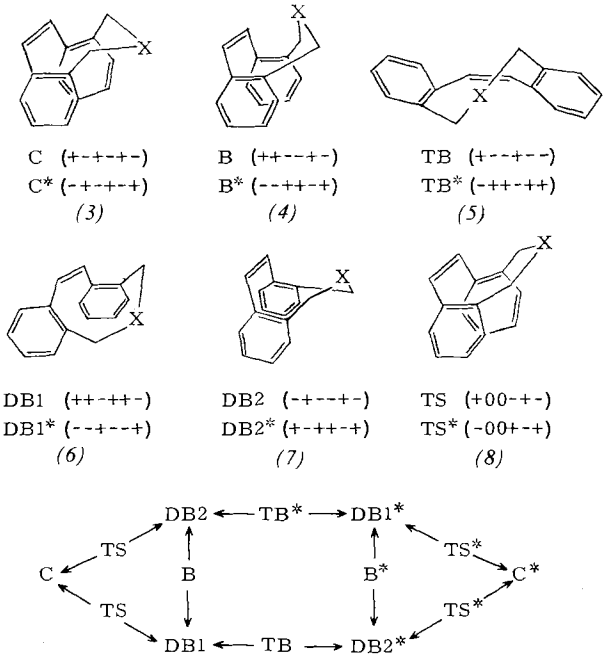


Fig. 1. Conformational changes in the hetero derivatives *(2b)*—*(2d)* of 12,13-dihydro-11*H*-dibenzo[*a*,*e*]cyclononene *(2a)*. The notation [1] for torsional angles refers in turn to the 13a-13, 13-12, 12-11, 11-10a, 6a-6, and 5-4a bonds.

Strain energy calculations show that the DB conformations [*(6)* and *(7)*] lie between[6] the B *(4)* and TB *(5)* conformations on the pseudorotational itinerary associated with all the Boat[3] conformations of the flexible boat family. The identification of the two ground state conformations [observed in the low temperature ^{1}H-NMR spectra of the aza derivatives *(2b)* and *(2c)*] as C and DB illustrates the importance of evaluating temperature-dependent ^{1}H-NMR spectra with collateral strain energy calculations. There is a satisfying correlation between the results observed for the two aza derivatives [*(2b)* and *(2c)*]. The *N*-methyl protons in *(2b)* and the α-protons of the *N*-benzyl groups in *(2c)* provide additional NMR probes and good agreement (Table 1) is attained for the C→Boat interconversions using two independent means of measurement.

Conformational analysis of the thia derivative *(2d)* in association with strain energy calculations showed that the nonbonded interactions between —S— and —CH=CH— would destabilize the DB conformation with respect to the C conformation *(3)* by 4.8 kcal/mol. Its ^{1}H-NMR spectrum showed (Table 1) that only the C conformation *(3)* was observably populated. The observed free energy of activation ($\Delta G^{\neq}$ = 15.5 kcal/mol) for C⇌C* inversion is in very satisfying agreement with the calculated strain energy difference (16.1 kcal/mol) between the C *(3)* and TS *(8)* conformations.

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CAS Registry Numbers:
(2b), 52826-37-6; *(2c)*, 52826-38-7; *(2d)*, 52826-39-8; *trans*-2,2'-stilbenedimethanol, 19132-49-1; *cis*-2,2'-stilbenedimethanol, 19132-47-9; *cis*-2,2'-bis(bromomethyl)stilbene, 52826-40-1; PBr_3, 7789-60-8.

[1] *R. Crossley, A. P. Downing, M. Nógrádi, A. Braga de Oliveira, W. D. Ollis,* and *I. O. Sutherland*, J. C. S. Perkin I *1973*, 105.

[2] *R. Gellatley, W. D. Ollis,* and *I. O. Sutherland*, in preparation.

[3] The description 'Chair' is non-specific and refers to both of the enantiomeric or degenerate conformations (C and C*) of the rigid chair type. Similarly, the description 'Boat' refers to any conformation of the flexible boat family. The descriptions, B, B*, TB, TB*, DB1, DB1*, DB2, DB2*, TS, and TS* used later in the communication are specific [1].

[4] *G. Wittig, H. Tenhaeff, W. Schoch,* and *G. Koenig*, Liebigs Ann. Chem. 572, 1 (1951).

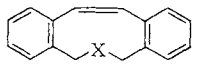
[5] *E. D. Bergmann* and *Z. Pelchowicz*, J. Amer. Chem. Soc. 75, 4281 (1953).

[6] For example, for the thia derivative *(2d)*, Φ_{56} = +48° and Φ_{67} = −98° in the DB1 conformation *(6)*.

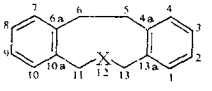
Conformational Studies on Aza and Thia Derivatives of 6,11,12,13-Tetrahydro-5*H*-dibenzo[*a*,*e*]cyclononene and 5,6,7,12,13,14-Hexahydrodibenzo[*a*,*f*]cyclodecene

By *W. David Ollis* and *J. Fraser Stoddart*[*]

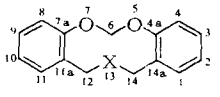
The examination[1] of the conformational behavior of the nine-membered ring olefins *(1)* has been extended to include the corresponding "6,9,6" systems *(2)* and "6,10,6" systems *(3)*. In comparison with compounds of type *(1)*, compounds *(2)* and *(3)* show a completely different kind of behavior.



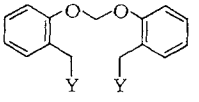
(1a), X = NCH_3
(1b), X = $NCH_2C_6H_5$
(1c), X = S



(2a), X = NH
(2b), X = NCH_3
(2c), X = $NCH_2C_6H_5$
(2d), X = $NCOCH_3$
(2e), X = S
(2f), X = SO_2



(3a), X = NCH_3
(3b), X = $NCH_2C_6H_5$
(3c), X = S
(3d), X = SO_2



(4a), Y = Br
(4b), Y = OH

The compounds *(2a)*—*(2f)* were prepared by standard methods (cf. Ref. [2]) from 1,2-bis(bromomethyldiphenyl)ethane[3]. Similarly, the dibromide *(4a)* (m.p. 125—127 °C), prepared (PBr_3) from the diol *(4b)*[4] gave the compounds *(3a)*—*(3d)*. It has been stated[2] that the room temperature ^{1}H-NMR spectrum of the secondary amine *(2a)* indicates that this compound has "a freely rotating ring system". We can be rather more explicit in our description of the conformational properties of the "6,9,6" systems *(2)* on the basis of the following results (Table 1).

Table 1. Properties, ^{1}H-NMR spectral parameters (100 MHz) in $CDCl_3$—CS_2 (1:1), and free energies of activation for ring inversion (C_2 chair $\rightleftarrows$ C_2 chair*) in the compounds of type *(2)* and *(3)* (T_c = coalescence temperature, $\nu_A - \nu_B$ = difference of the chemical shifts of H^A and H^B protons).

Compound	M.p. [°C]	Group	$\nu_A - \nu_B$ [Hz]	J_{AB} [Hz]	T_c [K]	ΔG^* at T_c [kcal/mol]
(2b)	63—65	11-CH_2, 13-CH_2	20.5	13.5	214	9.8
(2c)	108—110	*N*-α-benzyl	68.0 [a]	12.5 [a]	217 [a]	10.4 [a]
(2d) [b]	143—145	11-CH_2, 13-CH_2 [c]	230.0	13.5	215	9.8
			76.0	14.5	208	9.9
(2e)	110—111	11-CH_2, 13-CH_2	25.8	13.5	231	11.3
(2f)	220—221	11-CH_2, 13-CH_2	23.1	13.8	288	13.7
(3a)	oil [d]	12-CH_2, 14-CH_2	75.4	13.5	227	10.8
(3b)	95—97	*N*-α-benzyl	53.6	12.5	231	11.1
		12-CH_2, 14-CH_2	68.6	13.7	237	11.3
(3c)	103—104	12-CH_2, 14-CH_2	74.0	14.8	223	10.6
(3d)	239—240	12-CH_2, 14-CH_2	112.0	14.3	277	13.1

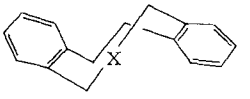
[a] Spectral parameters for the 11,11,13,13-tetradeuterio derivative since the protons H^{11} and H^{13} resonate with almost the same chemical shift as the *N*-α-benzyl protons.

[b] In CS_2.

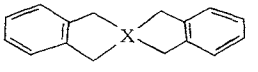
[c] The 11-CH_2 and 13-CH_2 groups in the amide are diastereotopic [5], and hence give rise to two AB systems, because of slow amide bond rotation in the temperature range where ring inversion is observed (cf. Ref. [10]).

[d] B.p. 120—130 °C at 0.05 torr.

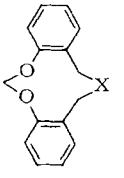
At low temperatures, the ^{1}H-NMR spectra of the compounds *(2b)*, *(2c)*, *(2e)*, and *(2f)* show a *single* AB system associated with either homotopic or enantiotopic[5] 11-CH_2 and 13-CH_2 groups. This requires that the observable ground state conformation must have either C_2 or C_s symmetry. A decision between these two possibilities is provided by the ^{1}H-NMR spectrum of the *N*-benzyl derivative *(2c)*, where below −50 °C, the α-benzyl protons are demonstrably diastereotopic[5]. Clearly, the ground state conformation must have C_2 symmetry leading to either a C_2 chair *(5)* or a C_2 twist-boat *(6)* as the only two possibilities[6]. Discrimination in favor of the C_2 chair *(5)* as the preferred conformation for the "6,9,6" systems *(2)* was shown by strain energy calculations on the sulfide *(2e)*[7]. Extrapolation to the other cases is justifiable.



C_2-chair (+−−+−+−)
C_2-chair* (−++−+−+)
(5)



C_2-boat (+−−++−+)
C_2-boat* (−++−−+−)
(6)



C_2-chair (−++−+−−+)
C_2-chair* (+−−+−++−)
(7)

We conclude that the magnitudes ($\Delta G^* = 9.8$—11.3 kcal/mol) of the free energies of activation for the ring inversion process (C_2 chair $\rightleftarrows$ C_2 chair*) for *(2b)*—*(2e)* are entirely in accord with a process involving torsion about single bonds. This is in contrast with the much higher values[1] ($\Delta G^* = 15.5$—16.3 kcal/mol) for the olefinic "6,9,6" systems *(1a)*—*(1c)* where angle strain is undoubtedly an important contributor in the transition state. The relatively high value ($\Delta G^* = 13.7$ kcal/mol) for the sulfone *(2f)* is mainly due to the much larger steric requirements of the SO_2 group in a torsional process.

The "6,10,6" systems *(3)* show entirely analogous behavior (Table 1). Compounds *(3a)*, *(3c)*, and *(3d)* all exhibit sharp singlets for their dioxymethylene protons at low temperatures.

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This observation is consistent with conformations having C_2 symmetry. For the *N*-benzyl derivative *(3b)* two AB systems, one for the 12-CH_2 and 14-CH_2 ring protons, and the other for the α-benzyl protons, are observed at low temperatures. Thus, the ground state conformation must have C_2 symmetry. The ^{1}H-NMR spectral changes (Table 1) indicate that inversion involving one observable conformation is clearly taking place and the ground state conformation which has been selected is the C_2 chair *(7)*[8]. Strain energy calculations have not been carried out because of the problems presented by several heteroatoms. However, the C_2 chair conformation *(7)* matches that selected by conformational analysis for monocyclic *cis-cis*-1,6-cyclodecadiene derivatives[9].

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CAS Registry Numbers:
(2b), 30115-78-7; *(2c)*, 31486-23-4; *(2d)*, 52810-62-5; *(2e)*, 52810-63-6; *(2f)*, 52810-64-7; *(3a)*, 52810-65-8; *(3b)*, 52873-51-5; *(3c)*, 52810-66-9; *(3d)*, 52810-67-0; *(4a)*, 52810-68-1; *(4b)*, 52810-69-2; PBr_3, 7789-60-8.

[1] *W. D. Ollis* and *J. F. Stoddart*, Angew. Chem. 86, 812 (1974); Angew. Chem. internat. Edit. 13, 728 (1974).

[2] *G. Pala, E. Crescenzi*, and *G. Bietti*, Tetrahedron 26, 5789 (1970).

[3] *E. D. Bergmann* and *Z. Pelchowicz*, J. Amer. Chem. Soc. 75, 4281 (1953).

[4] *W. Baker*, J. Chem. Soc. *1931*, 1765.

[5] *J. F. Stoddart* in *W. D. Ollis*: MTP International Review of Science, Organic Chemistry, Series One. Butterworths, London, 1973, Vol. 1, p. 1.

[6] The notation for torsional angles used in *(5)* and *(6)* refers in turn to the 13a-13, 13-12, 12-11, 11-10a, 6a-6, 6-5, and 5-4a bonds: *R. Crossley, A. P. Downing, M. Nógrádi, A. Braga de Oliveira, W. D. Ollis*, and *I. O. Sutherland*, J. C. S. Perkin I *1973*, 105.

[7] The C_2 chair was found to be 6.5 kcal/mol more stable than the C_2 twist-boat.

[8] The notation for torsional angles used in *(7)* refers in turn to the 14a-14, 14-13, 13-12, 12-11a, 7a-7, 7-6, 6-5, and 5-4a bonds.

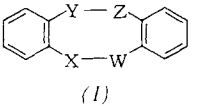
[9] *J. Dale, T. Ekeland*, and *T. Schaug*, Chem. Commun. *1968*, 1477; *H. L. Carrell, B. W. Roberts, J. Donohue*, and *J. J. Vollmer*, J. Amer. Chem. Soc. 90, 5263 (1968); *B. W. Roberts, J. J. Vollmer*, and *K. Servis*, *ibid.* 90, 5264 (1968); *A. Almenningen, C. G. Jacobsen*, and *H. M. Seip*, Acta Chem. Scand. 23, 1495 (1969); *A. Feigenbaum* and *J. M. Lehn*, Bull. Soc. Chim. Fr. *1969*, 3724; *J. Dale*, Pure Appl. Chem. 25, 469 (1971); *N. L. Allinger, M. T. Tribble*, and *J. T. Sprague*, J. Org. Chem. 37, 2423 (1972); *B. W. Roberts, J. J. Vollmer*, and *K. L. Servis*, J. Amer. Chem. Soc. 96, 4578 (1974).

[10] *R. J. Abraham, L. J. Kricka*, and *A. Ledwith*, J. C. S. Chem. Comm. *1973*, 282.

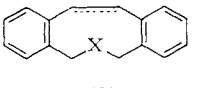
Conformational Studies on Oxa, Thia, and Aza Derivatives of 7,8,13,14-Tetrahydrobenzo[1,2]cyclononа[5,6,7-*de*]naphthalene and 8*H*, 15*H*-7,16-Dioxacyclodeca[1,2,3-*de*:6,7,8-*d'e'*]dinaphthalene

By *David J. Brickwood, W. David Ollis*, and *J. Fraser Stoddart*[*]

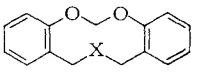
Recent results on the definition of the conformational behavior of hydrocarbons and heterocycles belonging to the "6,8,6" *(1)*[1,2], "6,9,6" *(2)*[3,4], and "6,10,6" *(3)*[4] systems by variable temperature ^{1}H-NMR studies and collateral strain energy calculations have encouraged the development of various complementary studies. These include the synthesis and examination of compounds *(4)* and *(5)*, in which an *ortho*-annelated benzene ring of *(2)* [cf. also *(1)* and *(3)*] is replaced by a *peri*-annelated naphthalene residue.



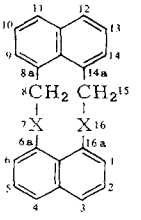
(1)



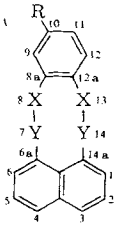
(2)



(3)



(6a), X = CH_2
(6b), X = O



(4a), R = H; X = CH_2; Y = CH_2
(4b), R = H; X = O; Y = CH_2
(4c), R = Me; X = O; Y = CH_2
(4d), R = H; X = S; Y = CH_2
(4e), R = Me; X = S; Y = CH_2
(4f), R = H; X = NMe; Y = CH_2
(4g), R = H; X = NTs; Y = CH_2

(5), R = H; X = CH_2; Y = O

In the heterocycles *(4b)*, *(4c)*, *(4f)*, *(4g)*, and *(5)*, we have observed (Table 1) an AB system at low temperatures for the ring methylene protons which coalesces to a sharp singlet at higher temperatures. This observation may be interpreted (Fig. 1) in terms of a ring inversion process involving conformations in which the methylene groups are related either by C_s symmetry [chair C *(7)* or boat B *(8)*] or by C_2 symmetry [twist-boat TB *(9)*]. Conformational analysis indicates that the *peri*-interaction between the methylene groups of the ring in the C *(7)* and B *(8)* conformations in compounds *(4b)*—*(4g)* is particularly large. This steric interaction is partially relieved in the TB conformation *(9)*; the principal nonbonded interactions in *(4b)*, *(4c)*, *(4f)*, and *(4g)* are between the methylene groups of the ring and the heteroatoms (X = O, NR'). We therefore propose that the TB conformation *(9)* is the ground state conformation observed and that ring inversion involves a TB⇌TB* pseudorotational process (Fig. 1). Three observations support this proposal: *(i)* The magnitude of the chemical shift differences ($\nu_A - \nu_B$) for the 7-CH_2 and 14-CH_2 protons is found (Tables 1 and 2) to depend significantly upon the nature of the ring heteroatoms. There are a number of examples[5] of van der Waals interactions between heteroatoms and proximate protons which lead to deshielding of the proton involved. The expectation[6] that the deshielding

Table 1. ^{1}H-NMR spectral parameters (100 MHz) and free energies of activation for ring inversion (TB⇌TB*) in compounds *(4b)*, *(4f)*, *(4g)*, *(5)*, and *(6b)* (T_c = coalescence temperature).

Compound	M.p. [°C]	Solvent	Prochiral group	$\nu_A - \nu_B$ [Hz]	J_{AB} [Hz]	T_c [K]	$\Delta G^{\neq}$ at T_c [kcal/mol]
(4b) [a]	125—127	$CDCl_3$—CS_2 (1:4)	OCH_2	33.0	11.1	194	9.5
(4f)	100—102	$CDCl_3$	NCH_2	241.0	14.0	303	14.0
(4g)	>320	$CDCl_3$	NCH_2	87.0	13.0	330	15.9
(5)	125—126	$CDCl_3$—CS_2 (1:2)	OCH_2	32.0	10.7	199	9.7
(6b)	214—215	$CDCl_3$—CS_2 (2:1)	OCH_2	28.6	10.0	212	10.4

[a] The singlet for the aryl methyl group in the 10-methyl derivative *(4c)* (m.p. 120—121 °C) remains sharp down to −100 °C, thus indicating the absence of exchange between diastereomeric conformations.

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Table 2. ^{1}H-NMR spectral changes (100 MHz) and activation parameters for compounds *(4d)* and *(4e)*.

Compound	M.p. [°C]	Solvent	Group	T [°C]	Chemical shifts (τ) [a] Coupling constants [Hz]	Sites involved in exchange [a]	$\Delta G^{\neq}$ [kcal/mol]	Process	Relative populations p_1	p_2
(4d)	195—197	$CDCl_3$:CS_2 (2:1)	SCH_2	−51	4.51 (A1), 5.72 (B1) [b], J 12.0 5.15 (A2), 5.53 (B2), J 14.0					
						A1→A2				
						B1→B2	13.3	TB→C	0.86	0.14
				−33	4.50 (A12), 5.73 (B12), J 12.0					
				+37	5.12 (AB12)	A1⇌B1	13.7	TB⇌TB*		
(4e)	272—274	$CDCl_3$	$ArCH_3$	−55	7.62 (A), 8.08 (B)	A→B	12.6	C→TB	0.80	0.20
				+30	8.01 (AB)	B→A	13.2	TB→C		

[a] Sites are designated (A) and (B) for uncoupled two-site systems; sites that represent two time-averaged signals are designated (AB). Sites are (A1), (B1), (A2), and (B2) for four-site systems where there is coupling in the form of two AB systems. Sites that represent two time-averaged signals are designated (AB1) [average of (A1) and (B1)] and A12 [average of (A1) and (A2)] *etc.*

[b] $\nu_{A1} - \nu_{B1} = 121$ Hz.

influence of heteroatoms will be related to their polarizabilities is also fulfilled by the data recorded in Tables 1 and 2; *(ii)* when the heteroatoms are both sulfur as in *(4d)* and *(4e)*, then transannular nonbonded interactions with the methylene groups of the ring destabilize the TB conformation *(9)* sufficiently to permit the observation of approximately 20% of a second conformation at low temperatures (Table 2). This minor conformation is presumably the C conformation *(7)*; *(iii)* the fact that the free energies of activation for the dithionins [*(4d)* and *(4e)*] and diazonins [*(4f)* and *(4g)*] are larger than those for the dioxonins [*(4b)* and *(4c)*] is consistent with the pseudorotational process shown in Figure 1, where the folded-boat (FB) conformations [*(10)* and *(11)*] correspond to the transition states. The main component of strain in these FB transition states must arise from nonbonded interactions between the methylene groups of the ring and the heteroatoms (X = O, S, NR').

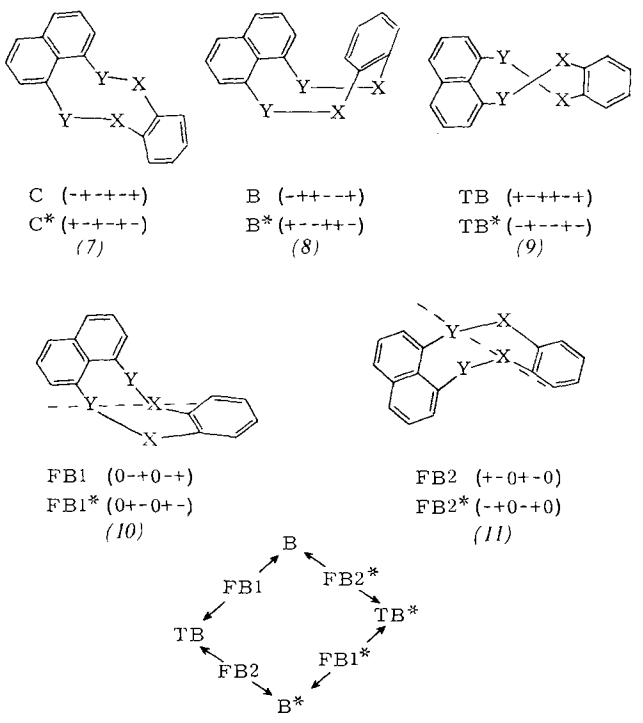


Fig. 1. Conformational changes in compounds *(4b)*, *(4c)*, *(4f)*, *(4g)*, and *(5)*. The notation [1] for torsional angles refers in turn to the 6a-7, 7-8, 8a-8, 12a-13, 13-14, and 14-14a bonds.

Similar considerations of chemical shift differences between the diastereotopic methylene protons (H^A and H^B) and the values of the free energies of activation for ring inversion (Table 1) in the dioxonin *(5)*, and in the dioxecin *(6b)*, also lead to very similar conclusions. The conformational itinerary of compounds *(5)* and *(6b)* also involve ring inversion (TB⇌TB*) between enantiomeric twist-boat conformations.

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CAS Registry Numbers:
(4b), 33296-36-5; *(4c)*, 52826-30-9; *(4d)*, 52826-31-0; *(4e)*, 52826-32-1; *(4f)*, 52826-33-2; *(4g)*, 52826-34-3; *(5)*, 52826-35-4; *(6b)*, 52826-36-5.

[1] *R. Crossley, A. P. Downing, M. Nógrádi, A. Braga de Oliveira, W. D. Ollis*, and *I. O. Sutherland*, J. C. S. Perkin I *1973*, 105.

[2] *M. Montecalvo, M. St. Jacques*, and *R. Wasylishen*, J. Amer. Chem. Soc. *95*, 2023 (1973); *D. J. Brickwood, W. D. Ollis*, and *J. F. Stoddart*, unpublished results; *W. D. Ollis* and *J. F. Stoddart*, J. C. S. Chem. Comm. *1973*, 571; *A. Saunders* and *J. M. Sprake*, J. C. S. Perkin II *1972*, 1660.

[3] *W. D. Ollis* and *J. F. Stoddart*, Angew. Chem. *86*, 812 (1974); Angew. Chem. internat. Edit. *13*, 728 (1974).

[4] *W. D. Ollis* and *J. F. Stoddart*, Angew. Chem. *86*, 813 (1974); Angew. Chem. internat. Edit. *13*, 730 (1974).

[5] *S. Winstein, P. Carter, F. A. L. Anet*, and *A. J. R. Bourn*, J. Amer. Chem. Soc. *87*, 5239 (1965); *C. R. Johnson* and *D. C. Vegh*, Chem. Commun. *1969*, 557; *T. Sato* and *K. Uno*, J. C. S. Perkin I *1973*, 895.

[6] *L. M. Jackman* and *S. Sternhell*: Applications of Nuclear Magnetic Resonance Spectroscopy to Organic Chemistry. Pergamon, London 1969, p. 71.

A Heptalene Synthesis from 1,6-Methano[10]annulene; Evidence for a Fast π-Bond Shift

By *Emanuel Vogel, Heinrich Königshofen, Jürgen Wassen, Klaus Müllen*, and *Jean F. M. Oth*[*]

Heptalene *(1)*, which like its homolog pentalene[1] has long been the subject of theoretical study, was synthesized by *Dauben* and *Bertelli*[2] in 1961. However, it remained poorly accessible and to this day the bonding of the hydrocarbon has still not been thoroughly characterized by experimental means. Recent quantum mechanical calculations[3] indicate that the heptalene structure having delocalized π-bonds (D_{2h} molecular symmetry) is destabilized by comparison with the structure possessing alternating bonds (C_s symmetry). By ana-

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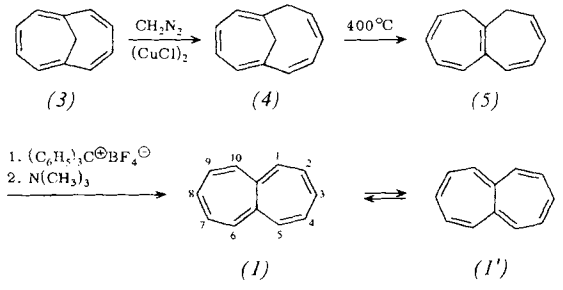
logy with the situation observed in [4*n*]annulenes[4], *(1)* was therefore expected to display the phenomenon of a fast π-bond shift.



(1) *(2)*

Our latest studies on the [4*n*]annulene 1,7-methano[12]annulene *(2)*[5], which is derived from heptalene by insertion of a CH_2 group into the 1,7-bond, prompted us to reconsider the question of the bonding in *(1)* and to undertake detailed chemical and spectral comparisons between the two 12π-electron systems. We have now found an improved entry to *(1)* and succeeded in detecting the fast π-bond shift postulated for *(1)*.

The new heptalene synthesis starts from 1,6-methano[10]annulene *(3)*[6]. As already reported[7], $(CuCl)_2$-catalyzed reaction of *(3)* with diazomethane affords bicyclo[5.4.1]-dodeca-1(11),2,4,7,9-pentaene *(4)*, a product of isomerization of the cyclopropane hydrocarbon formed by CH_2 addition to the 1,2-bond of *(3)*, alongside tetracyclo[5.4.1.0.$0^{2,4}$]dodeca-5,8,10-triene[8]. If *(4)* is subjected to pyrolysis at 400 °C *(in vacuo)* in a pyrex tube filled with quartz chips, a mixture of dihydroheptalenes is formed which contains *(5)* and its C_{2h}-symmetry isomer as principal components. Tetracyclo[5.4.1.0.$0^{2,4}$]dodeca-5,8,10-triene, too, furnishes dihydroheptalenes under the above pyrolysis conditions. Thermal isomerization of the two hydrocarbons clearly proceeds *via* a Berson-Willcott rearrangement[9]. The dihydroheptalene mixture cleanly affords heptalene *(1)* on Dauben dehydrogenation[2]. The hydrocarbon, which displays a pronounced tendency to undergo polymerization and for which no physical constants were previously known, was obtained as brownish red crystals having m.p. 10—12 °C (platelets from methanol).



(3) *(4)* *(5)*

(1) *(1')*

The ^{1}H-NMR spectrum of *(1)*, not formerly investigated for temperature dependence[10], displays an AA'BB'C system corresponding to a heptalene structure with D_{2h} molecular symmetry[11]. No decision can be reached from the observed spectral type whether the π-bonds of *(1)* are delocalized or localized and subject to fast fluctuation.

The ^{13}C-NMR spectrum of *(1)* recorded at −30 °C (Fig. 1a) contains four signals of relative intensity 2:4:2:4, thus demonstrating D_{2h} symmetry in accord with the ^{1}H-NMR spectrum. Signal assignment followed from the ^{13}C—H coupling constants and from the way in which the spectrum changes with temperature. The existence of a fast π-bond shift in *(1)* should be manifested in a splitting of the C^1/C^5 and C^2/C^4 signals into two peaks each on lowering of the temperature, *i.e.* by a change from the 4-line to a 6-line spectrum. The pertinent signals do indeed exhibit gradual broadening below −120 °C, but a further drop in temperature to −160 °C (coalescence) is required for the expected splitting to occur. Remarkably, even at −167 °C, the lowest temperature reached, a certain exchange broadening is still to be observed (Fig. 1b). This ^{13}C-NMR finding constitutes the first experimental proof of the theoretically required bond alternation in heptalene and of a fast π-bond shift corresponding to *(1)*⇌*(1')*.

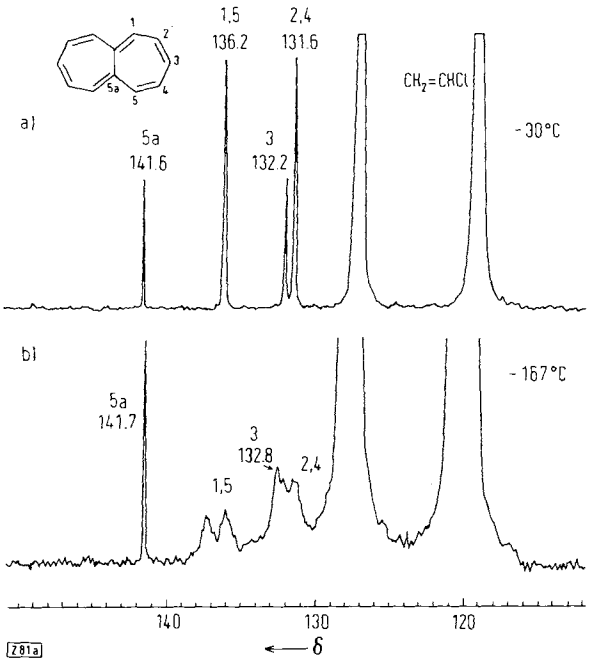
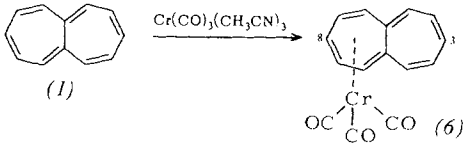


Fig. 1. ^{1}H broad band decoupled ^{13}C-NMR spectra of heptalene *(1)* at a) −30 °C and b) −167 °C [in vinyl chloride/dichloromethane (5:1) with TMS as internal standard].

An activation energy of about 3.5 kcal/mol could be established for the π-bond shift by line shape analysis of the spectra in the temperature range −130 to −167 °C and evaluation of the resulting rate constants according to the Arrhenius equation. Surprisingly, this value is considerably lower than would be expected from the destabilization energy of 12 kcal/mol[3] calculated for heptalene with D_{2h} symmetry[12].



(1) *(6)*

Treatment of heptalene *(1)* with tris(acetonitrile)tricarbonylchromium in tetrahydrofuran (room temperature; 1 h) affords the tricarbonylchromium complex *(6)*[13] [blackish brown platelets from hexane; m.p. 110 °C (dec.); yield 70%] which is stable in the crystalline state; treatment with bis(2-aminoethyl)amine regenerates the hydrocarbon. Although the ^{1}H-NMR spectrum of *(6)* is relatively complicated, double resonance experiments[14] clearly indicate a proton ratio of 1:2:2:2:2:1. Hence the complex must possess C_s symmetry (plane of symmetry through C^3, C^8, and Cr). Nothing can yet be said about the way in which this symmetry arises, particularly since no evidence has yet been found for temperature dependence of the NMR spectrum.

Reduction of *(1)* with lithium in tetrahydrofuran leads to the aromatic heptalene dianion[15] [NMR (D_8-THF): doublet at τ = 2.6 (H^1, H^5), triplet at τ = 4.4 (H^2, H^4), and triplet at τ = 3.9 (H^3)], which can be regarded as the 14π analog of the pentalene dianion[16].

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CAS Registry Numbers:
(1), 257-24-9; *(1)*-dianion, 52827-30-2; *(3)*, 2443-46-1; *(4)*, 28172-97-6; *(5)*, 52781-65-4; *(6)*, 52827-29-9; tris(acetonitrile)tricarbonylchromium, 16800-46-7

[1] *K. Hafner*, Pure Appl. Chem. *28*, 153 (1971); *K. Hafner, R. Dönges, E. Goedecke*, and *R. Kaiser*, Angew. Chem. *85*, 362 (1973); Angew. Chem. internat. Edit. *12*, 337 (1973); *K. Hafner* and *H. U. Süss*, Angew. Chem. *85*, 626 (1973); Angew. Chem. internat. Edit. *12*, 575 (1973); *R. Bloch, R. A. Marty*, and *P. de Mayo*, J. Amer. Chem. Soc. *93*, 3071 (1971); Bull. Soc. Chim. Fr. *1972*, 2031.

[2] *H. J. Dauben, Jr.* and *D. J. Bertelli*, J. Amer. Chem. Soc. *83*, 4659 (1961).

[3] *G. Binsch* in *E. D. Bergmann* and *B. Pullman:* The Jerusalem Symposia on Quantum Chemistry and Biochemistry, Vol. III, p. 25 (1971); *T. Nakajima, A. Toyota*, and *H. Yamaguchi, ibid.* p. 227 and references cited therein; *T. Nakajima*, Fortschr. Chem. Forsch. *32*, 1 (1972).

[4] *J. F. M. Oth*, Pure Appl. Chem. *25*, 573 (1971); *R. C. Haddon, V. R. Haddon*, and *L. M. Jackman*, Fortschr. Chem. Forsch. *16*, 103 (1971).

[5] *E. Vogel, H. Königshofen, K. Müllen*, and *J. F. M. Oth*, Angew. Chem. *86*, 229 (1974); Angew. Chem. internat. Edit. *13*, 281 (1974).

[6] Detailed synthetic procedure: *E. Vogel, W. Klug*, and *A. Breuer*, Org. Synth., in press.

[7] *W. Grimme, H. Hoffmann*, and *E. Vogel*, Angew. Chem. *77*, 348 (1965); Angew. Chem. internat. Edit. *4*, 354 (1965); *E. Vogel, R. Feldmann*, and *H. Düwel*, Tetrahedron Lett. *1970*, 1941.

[8] *E. Vogel*, XXIIIrd International Congress of Pure and Applied Chemistry, Special Lectures, Vol. 1, p. 275 (1971).

[9] *J. A. Berson*, Accounts Chem. Res. *1*, 152 (1968).

[10] Our own observations indicate that the ^{1}H-NMR spectrum of *(1)* is temperature dependent between -130 and -167 °C. However, ^{13}C-NMR spectroscopy was required to establish the dynamic process responsible as a π-bond shift.

[11] Concerning analysis of the room temperature ^{1}H-NMR spectrum of *(1)*, see *D. J. Bertelli* in *E. D. Bergmann* and *B. Pullman:* The Jerusalem Symposia on Quantum Chemistry and Biochemistry, Vol. III, p. 326 (1971).

[12] The reasons for this striking discrepancy are presently under investigation.

[13] Professor *O. S. Mills* (Manchester) is currently performing an X-ray structure analysis of the complex.

[14] We are grateful to Dr. *G. Ulmen* for these measurements.

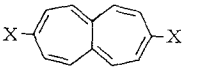
[15] *J. F. M. Oth, K. Müllen*, and *E. Vogel*, to be published.

[16] *T. J. Katz, M. Rosenberger*, and *R. K. O'Hara*, J. Amer. Chem. Soc. *86*, 249 (1964).

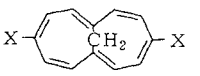
Stable Heptalenes—3,8-Dibromoheptalene

By *Emanuel Vogel* and *Joachim Ippen*[*]

Heptalene [*(1)*, X=H][1,2] and the structurally closely related 1,7-methano[12]annulene [*(2)*, X=H][3] are low-melting polyene hydrocarbons displaying a pronounced tendency to undergo polymerization. For projected X-ray structural investigations on the heptalene and 1,7-methano[12]annulene systems it appeared desirable to have stable crystalline derivatives of the two hydrocarbons at our disposal. Experience from annulene chemistry suggested that little more than symmetrical disubstitution (by halogen, carboxyl, or *tert*-butyl), preferably in positions 3,8 or 4,10, would suffice in the case of heptalene and 1,7-methano[12]annulene to afford compounds having the desired properties. Whereas attempts to prepare symmetrically substituted heptalenes and 1,7-methano[12]annulenes from the parent hydrocarbons have so far remained unsuccessful, compounds of structural type *(1)* and *(2)*[4] have now been obtained by directed syntheses. We shall here describe the preparation of 3,8-dibromoheptalene *(10)*.



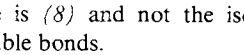
(1)



(2)

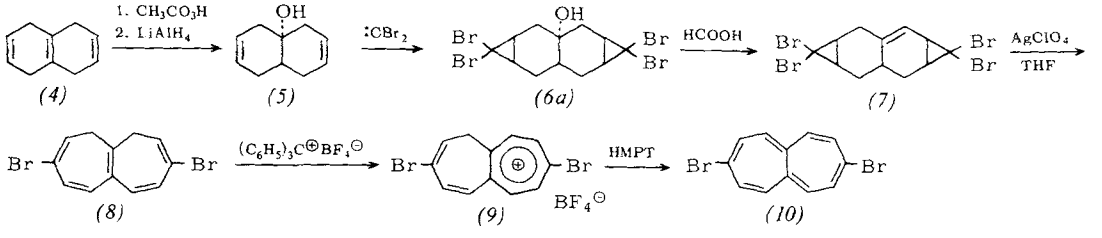
Our synthetic concept for *(10)* invoked the bis-adducts *(3a)* and *(3b)* of dibromocarbene to the outer double bonds of isotetralin *(4)*, which are inaccessible by direct methods, as key intermediates. It therefore became necessary to protect the central double bond of *(4)* which is more reactive toward dibromocarbene. This was accomplished by converting *(4)* into the known 4a,8a-epoxy-1,4,4a,5,8,8a-hexahydronaphthalene by peracetic acid, and reducing it to the alcohol *(5)* with $LiAlH_4$. Reaction of *(5)* with bromoform (fivefold excess) and 50% aqueous sodium hydroxide by *Mąkosza*'s method[5] yielded a mixture of stereoisomeric bis-adducts from which *(6a)* [m.p. 168—169 °C (dec.); yield 40%] and *(6b)* [m.p. 185—187 °C (dec.); yield 13%] having their three-membered rings oriented *trans-trans* and *cis-trans*[6], respectively, to the OH group could be isolated by fractional crystallization. On heating with anhydrous formic acid, *(6a)* furnished an olefinic product almost quantitatively; the NMR spectrum showed this product to contain 39% of *(3a)* and 61% of *(7)*[7]. Since separation of the two isomers ran into difficulties, the mixture was treated with silver perchlorate in anhydrous tetrahydrofuran (70 °C; 2 h). *(7)* reacted to form dibromodihydroheptalene *(8)*, while *(3a)* surprisingly remained practically unchanged. Isolation of *(8)* [m.p. 118—120 °C (dec.); yield 32%] and *(3a)* [m.p. 180—181 °C (dec.)] was accomplished by chromatography on silica gel (elution with pentane). The ^{13}C-NMR spectrum shows unequivocally, from the non-equivalence of the C atoms of the central double bond, that the dibromodihydroheptalene is *(8)* and not the isomer having through-conjugated double bonds.

Dehydrogenation of *(8)* with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, which has proved of value in the synthesis of 1,7-methano[12]annulene[13], was unsatisfactory. We therefore resorted to *Dauben*'s method[1,8] and converted *(8)* first into



(3a) cis
(3b) trans

the tropylium salt *(9)* (yield 96%) by treatment with triphenylmethyl tetrafluoroborate in dichloromethane (room temperature; 45 min). The best results in the subsequent deprotonation of *(9)* to *(10)* have so far been achieved by stirring the salt at room temperature in hexamethylphosphoric amide (HMPT) for 30 min. After recrystallization from ether, compound *(10)* was obtained as beautiful dark brown crystals (needles) having m.p. 100 °C (dec.) (yield 56%) and which are completely stable to atmospheric oxygen at room temperature.



(4) *(5)* *(6a)* *(7)* *(8)* *(9)* *(10)*

In accord with structure *(10)*, the ^{1}H-NMR spectrum of the compound displays only an AB system at $\tau = 3.74$ and 4.89 ($J = 9.5$ Hz). Since proof of a fast π-bond shift has recently

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been provided by ^{13}C-NMR spectroscopy for heptalene[2], there can be no doubt that the simplicity of the ^{1}H-NMR spectrum of *(10)* is likewise due to a dynamic process of this kind and not to delocalization of the 12π system. The UV spectrum of *(10)* [λ_{max} (cyclohexane) = 250 (ε = 23400 sh), 266 (26350), 356 nm (7200)] shows a slight red shift compared to that of the parent compound, as would be expected from the influence of the bromine substituents.—Detailed studies on *(10)* and other heptalenes derivable therefrom are in progress.

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CAS Registry Numbers:
(3a), 52781-70-1; *(4)*, 493-04-9; *(5)*, 52781-71-2; *(6a)*, 52842-93-0; *(6b)*, 52882-38-9; *(7)*, 52781-72-3; *(8)*, 52781-73-4; *(9)*, 52842-95-2; *(10)*, 52781-74-5

[1] *H. J. Dauben, Jr.* and *D. J. Bertelli*, J. Amer. Chem. Soc. *83*, 4657, 4659 (1961).

[2] *E. Vogel, H. Königshofen, J. Wassen, K. Müllen*, and *J. F. M. Oth*, Angew. Chem. *86*, 777 (1974); Angew. Chem. internat. Edit. *13*, 732 (1974).

[3] *E. Vogel, H. Königshofen, K. Müllen*, and *J. F. M. Oth*, Angew. Chem. *86*, 229 (1974); Angew. Chem. internat. Edit. *13*, 281 (1974).

[4] *E. Vogel et al.*, to be published.

[5] *M. Mąkosza* and *M. Wawrzyniewicz*, Tetrahedron Lett. *1969*, 4659.

[6] The configuration of *(6a)* follows from the assumption that the two three-membered rings in the bisadduct of dibromocarbene to 4a,8a-epoxy-1,4,4a,5,8,8a-hexahydronaphthalene are *trans* to the epoxide ring; *(6a)* can be transformed *via (3a)* into the epoxy compound.

[7] The bisadduct *(6b)* gives *(3b)* as sole product on dehydration with anhydrous formic acid.

[8] *H. J. Dauben, Jr., L. R. Honnen*, and *K. M. Harmon*, J. Org. Chem. *25*, 1442 (1960).

Dimethyl 3,8-Heptalenedicarboxylate

By *Emanuel Vogel* and *Frank Hogrefe*[*]

The synthesis of 3,8-dibromoheptalene[1] suggests that bis-outer adducts of carbenes to isotetralin *(1)*, *i.e.* tetracyclo[5.5.0.0^{3,5}.0^{9,11}]dodec-1(7)-enes, might be generally applicable as starting compounds for preparing heptalenes. While use of dihalocarbenes as carbene components necessitates blocking of the electron-rich central double bond of *(1)*, such a measure is not required on use of the alkoxycarbonylcarbenes which are more reactive and therefore preferentially attack the outer double bonds of *(1)*[2, 3]. From these considerations results a relatively simple entry to dimethyl 3,8-heptalenedicarboxylate.

The reaction of isotetralin *(1)* (0.75 mol) with ethyl diazoacetate (2 mol) in the presence of copper powder (5 g), performed by slow dropwise addition (96 h) of the diazo compound to the isotetralin/copper mixture at 100 °C, afforded a complex product from which a fairly pure 2:1 adduct crystallized after 24 hours' standing; recrystallization from ethanol led to a sterically uniform diethyl tetracyclo[5.5.0.0^{3,5}.0^{9,11}]dodec-1(7)-ene-4,10-dicarboxylate having m.p. 196—197 °C (yield 18 %)[4]. The diethyl ester is readily transformed into the dimethyl ester *(2)* [m.p. 171—172 °C (from methanol); yield 84 %] by alkaline hydrolysis and subsequent esterification of the crude acid with diazomethane. The stereochemistry of *(2)* has not yet been elucidated with regard to the arrangement of the three-membered rings; however, several analogous cases[5] strongly indicate both methoxycarbonyl groups to be in the *exo* position.

Reaction of *(2)* with a 4.5-fold molar amount of *N*-bromosuccinimide (NBS) with addition of azobutyronitrile in boiling carbon tetrachloride (reaction duration 45 min) furnishes a bromination product consisting mainly of the tetrabromide *(3)* (presumably a mixture of stereoisomers), yield *ca.* 55 %. Compound *(3)*, which was not isolated pure, can be smoothly dehalogenated to *(4)* by refluxing with activated zinc dust in tetrahydrofuran. Work-up of *(4)* was by chromatography on a short alumina column (dichloromethane) and recrystallization from *n*-hexane [m.p. 130—132 °C (dec.); yield 60%; UV (cyclohexane): λ_{max} = 230 (ε = 36700), 235 (38600), 296 nm (6100)]. After an initial unsuccessful attempt to dehydrogenate *(4)* to *(5)* *via* the tropylium ion[1, 6], reaction with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) in benzene at 160 °C (ampoule; 15 min)[7] led to the desired result. The product *(5)* could be readily isolated by chromatography (silica gel; dichloromethane) and precipitated as brownish red needles on recrystallization from ether; m.p. 142—143 °C (yield 29%). Remarkably, *(5)* is stable to air at room temperature.

The spectral properties of *(5)* largely resemble those of 3,8-dibromoheptalene [60 MHz ^{1}H-NMR spectrum ($CDCl_3$): AB system at τ = 3.30 and 4.82 with J = 10.5 Hz (vinylic protons), singlet at τ = 6.25 (—$COOCH_3$ protons) (intensity ratio 4:3); UV spectrum (cyclohexane) λ_{max} = 262 (ε = 24800), 398 (9700), 547 nm (270, sh)].

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CAS Registry Numbers:
(1), 493-04-9; *(2)*, 52781-66-5; *(3)*, 52920-68-0; *(4)*, 52781-67-6; *(5)*, 52781-68-7;
diethyl tetracyclo[5.5.0.0^{3,5}.0^{9,11}]dodec-1(7)-ene-4,10-dicarboxylate, 52781-69-8

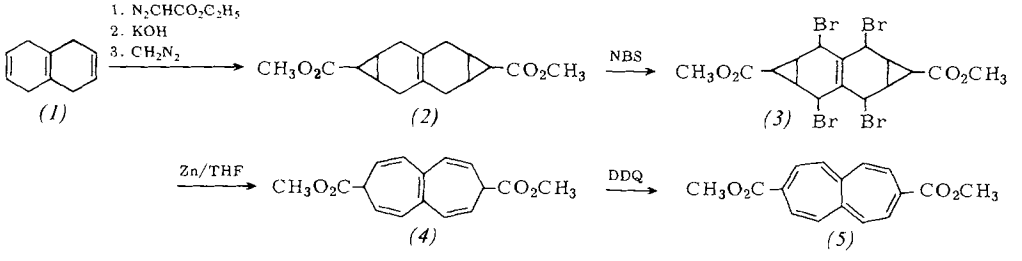
[1] *E. Vogel* and *J. Ippen*, Angew. Chem. *86*, 778 (1974); Angew. Chem. internat. Edit. *13*, 734 (1974).

[2] Unpublished experiments in collaboration with *H. Lepper*; see also *G. L. Thompson, W. E. Heyd*, and *L. A. Paquette*, J. Amer. Chem. Soc. *96*, 3177 (1974).

[3] *W. Kirmse*: Carbene Chemistry. 2nd Edit. Academic Press, New York 1971, p. 288.

[4] The steric homogeneity and high symmetry of the adduct is indicated primarily by its extremely simple ^{13}C-NMR spectrum.

[5] See, *e.g.*, *H. Musso* and *U. Biethan*, Chem. Ber. *97*, 2282 (1964).



(1) *(2)* *(3)* *(4)* *(5)*

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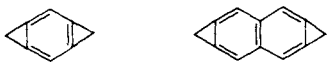
[6] *H. J. Dauben, Jr.* and *D. J. Bertelli*, J. Amer. Chem. Soc. *83*, 4657 (1961).

[7] *E. Vogel, H. Königshofen, K. Müllen*, and *J. F. M. Oth*, Angew. Chem. *86*, 229 (1974); Angew. Chem. internat. Edit. *13*, 281 (1974).

1,4-Dihydrodicyclopropa[*b*,*g*]naphthalene

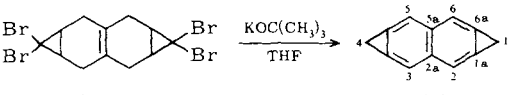
By *Joachim Ippen* and *Emanuel Vogel*[*]

The cyclopropa-arenes cyclopropabenzene[1-3] and cyclopropa[*b*]naphthalene[4] are relatively stable compounds without pronounced bond fixation, although the presence of the three-membered ring gives rise to extensive strain and distortion of the benzene rings[5,6]. It therefore appeared conceivable that cyclopropa-arenes having more than one three-membered ring might also be capable of existence, *e. g.* 1,3-dihydrodicyclopropa[*a*,*d*]benzene *(1)* and 1,4-dihydrodicyclopropa[*b*,*g*]naphthalene *(2)*. As we found, at least compound *(2)* is isolable.



(1) *(2)*

The *cis-trans* isomeric 4,4,10,10-tetrabromotetracyclo[5.5.0.0^{3,5}.0^{9,11}]dodec-1(7)-enes [*(3a)* and *(3b)* respectively] which we encountered in the synthesis of heptalenes[7] provided us with an opportunity of directly obtaining compound *(2)* by the action of strong bases (*Billups'* method[2]). On treatment of *(3a)* or *(3b)* with a tenfold excess of potassium *tert*-butoxide in tetrahydrofuran (room temperature, 4h), clean dehydrohalogenation does in fact take place, forming the desired compound *(2)* in both cases. The new cyclopropa-arene was obtained after chromatography on alumina (elution with pentane) and subsequent recrystallization from ether as slightly yellow tinted rhombic crystals (yield 30 and 33%, respectively) which undergo explosive decomposition at 132—133 °C. Since the crystals are also sensitive to shock their handling requires caution.



(3a), *cis*
(3b), *trans*

(2)

Proof of the structure of 1,4-dihydrodicyclopropa[*b*,*g*]naphthalene *(2)* follows from the spectra and chemical properties of the compound. The ^{1}H-NMR spectrum shows only two signals at $\tau = 2.41$ and 6.48 (intensity ratio 1:1) and thus corresponds in shape and position of the signals to that expected for aromatic *(2)*. The ^{13}C-NMR spectrum [$CCl_4/CDCl_3$; TMS: $\delta(C^{1a}/C^{6a}) = 122.8$, $\delta(C^2/C^6) = 113.5$, $\delta(C^{2a}/C^{5a}) = 140.1$, $\delta(C^1) = 19.9$ ppm] is informative since it largely accords with that of cyclopropabenzene[8] with regard to the resonance frequencies of C^{1a}/C^{6a}, C^2/C^6, and C^1, and the coupling constant $^1J(1, H) = 170$ Hz. Justification for regarding *(2)* and cyclopropa[*b*]naphthalene as true naphthalene derivatives is provided by the UV spectrum [λ_{max} (cyclohexane) = 226 ($\varepsilon = 74200$), 273 (7050), and 326 nm (6000) (B_b, L_a, L_b bands)[9]]; the only significant difference from that of naphthalene lies in the enhanced intensity of the L_b band. The IR spectrum [CCl_4: 1622 cm^{-1} (aromatic double bond)] and the mass spectrum are likewise in excellent accord with the structure assumed.

Like cyclopropabenzene and cyclopropa[*b*]naphthalene, *(2)* is sensitive to acidic reagents[10]. As an example we cite the extremely fast reaction of *(2)* with acetic acid in the presence of $Ag^{\oplus}$ ion, which leads expectedly to a mixture of 2,6- and 2,7-naphthalenedimethyl diacetate.

According to thermochemical studies by *Billups et al.*, cyclopropa[*b*]naphthalene is destabilized by 67.8 kcal/mol (sum of strain energy and resonance loss) compared with the strain-free aromatic model[6]. Hence it can be reasonably assumed that the corresponding destabilization energy will considerably exceed 100 kcal/mol in the case of *(2)*. Since *(2)* itself already tends to undergo explosive decomposition, it may well be that the limit of existence at room temperature has been reached in *(1)*, where the possibility of a certain internal equalization of strain is even less favorable than in *(2)*.

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CAS Registry Numbers:
(2), 52781-75-6; *(3a)*, 52781-70-1; *(3b)*, 52882-39-0

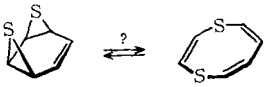
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[1] *E. Vogel, W. Grimme*, and *S. Korte*, Tetrahedron Lett. *1965*, 3625.
[2] *W. E. Billups, A. J. Blakeney*, and *W. Y. Chow*, Chem. Commun. *1971*, 1461.
[3] *P. Radlick* and *H. T. Crawford*, J. C. S. Chem. Comm. *1974*, 127.
[4] *W. E. Billups* and *W. Y. Chow*, J. Amer. Chem. Soc. *95*, 4099 (1973).
[5] *E. Carstensen-Oeser, B. Müller*, and *H. Dürr*, Angew. Chem. *84*, 434 (1972); Angew. Chem. internat. Edit. *11*, 422 (1972).
[6] *W. E. Billups, W. Y. Chow, K. H. Leavell, E. S. Lewis, J. L. Margrave, R. L. Sass, J. J. Shieh, P. G. Werness*, and *J. L. Wood*, J. Amer. Chem. Soc. *95*, 7878 (1973).
[7] *E. Vogel* and *J. Ippen*, Angew. Chem. *86*, 778 (1974); Angew. Chem. internat. Edit. *13*, 734 (1974).
[8] *H. Günther, G. Jikeli, H. Schmickler*, and *J. Prestien*, Angew. Chem. *85*, 826 (1973); Angew. Chem. internat. Edit. *12*, 762 (1973).
[9] *J. R. Platt*, J. Chem. Phys. *17*, 484 (1949).
[10] See the review by *B. Halton*, Chem. Rev. *73*, 113 (1973).

syn-Benzene Bisepisulfide (*syn*-3,4:5,6-Bis(epithio)-1-cyclohexene)[**]

By *Emanuel Vogel, Erich Schmidbauer*, and *Hans-Josef Altenbach*[*]

The still unknown 10π-heterocycle 1,4-dithiocin *(2)*, which is to be regarded as a potential aromatic compound according to the Hückel rule, has been the goal of several synthetic attempts[1,2] and the subject of quantum mechanical calculations[3,4] during recent years. Whereas the experimental work on *(2)* is not very informative with regard to its π-electron structure, Hückel calculations—employing Coulomb and resonance integrals derived from thermodynamic data for divalent sulfur—predict, contrary to expectations, that *(2)* will not possess pronounced electronic stability[4]. As already discussed previously[5,6], symmetry-allowed valence isomerization ($_\pi 2_s + _\sigma 2_s + _\sigma 2_s$ process) of *syn*-benzene bisepisulfide *(1)* constitutes an apparently compelling synthetic route to *(2)*, provided that the eight-membered heterocycle is aromatic. In the present communication we report about compound *(1)*, the first arene episulfide to have been prepared, and its thermal behavior.



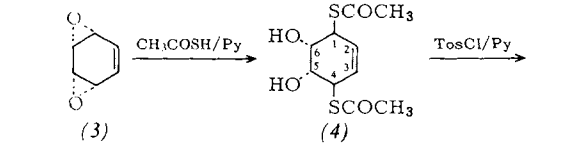
(1) *(2)*

A suitable starting material for attempted synthesis of *(1)* was *syn*-benzene dioxide *(3)*, which we described in a recent

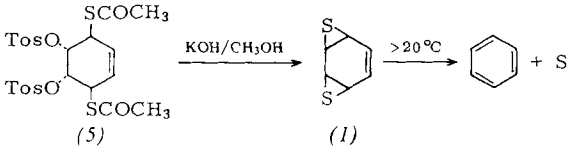
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publication[7]. Reaction of a solution of *(3)* in pyridine at 0°C with thioacetic acid affords *S,S*-(5,6-dihydroxy-2-cyclohexen-1,4-ylene) bis(thioacetate) [colorless crystals from diisopropyl ether, m.p. 117°C, yield 13%] whose NMR spectrum [($CDCl_3$): $\tau = 4.32$ (d, H-2, H-3), 5.65 (dd, H-1, H-4), 6.05 (d, H-5, H-6), 7.6 (s, CH_3)] shows the *1r,4c,5t,6t* compound analogous to conduritol A[8] to be present. On reaction with *p*-toluenesulfonyl chloride in pyridine (0°C), compound *(4)* gives the ditosylate *(5)* [needles from dichloromethane/pentane, m.p. 172—173°C (dec.), yield 60%]. Subsequent treatment of *(5)* in dichloromethane at −20°C with a fivefold excess of KOH in methanol leads smoothly to the desired *syn*-benzene bisepisulfide (*syn*-3,4 : 5,6-bis(epithio)-1-cyclohexene) *(1)* which is obtained as a crystalline mass after filtration of the reaction solution over a 10-cm alumina column at −20°C and evaporation of the solvent at 0°C. Recrystallization from ether at low temperature afforded colorless needles [m.p. 34—36°C (dec.), yield 80%; mass spectrum: $m/e = 142$ (M^+), 110 ($M^+ - S$), 78 ($M^+ - 2S$, 100%)].



(3) *(4)*



(5) *(1)*

The ^{1}H-NMR spectrum ($CDCl_3$) of *(1)* reproduced in Figure 1 shows a triplet at $\tau = 3.66$ (H-1, H-2) and multiplets at $\tau = 6.11$ (H-4, H-5) and 6.46 (H-3, H-6). Assignment of the episulfide protons, according to which the upfield multiplet is due to the allylic protons H-3 and H-6, is based on double resonance experiments such as have been described previously for *(3)*[7]. In order to determine the coupling constants of the episulfide protons the sample was irradiated at the resonance frequency of the olefinic protons and the resulting AA'BB' system analyzed; the values obtained were $J_{3,4} = 5.94$ Hz, $J_{3,5} = 0.49$ Hz, $J_{3,6} = 0.23$ Hz, and $J_{4,5} = 6.14$ Hz. The high value of $J_{4,5}$ appears significant because it supports the *syn* configuration of the benzene bisepisulfide which so far follows solely from the synthetic pathway[9].

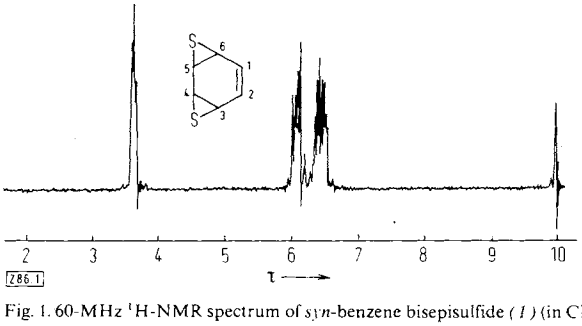
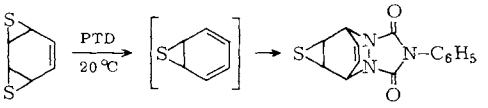


Fig. 1. 60-MHz ^{1}H-NMR spectrum of *syn*-benzene bisepisulfide *(1)* (in $CDCl_3$ at −20°C; TMS as internal standard).

syn-Benzene bisepisulfide is thermolabile. Its solutions in carbon disulfide or chloroform decompose at 20°C with a half-life of about 30 min (determined by NMR spectroscopy) to form benzene and sulfur as final products. Decomposition in the presence of 4-phenyl-1,2,4-triazoline-3,5-dione (PTD) gave a 10% yield of the Diels-Alder adduct *(7)* of benzene episulfide *(6)* [m.p. 157—158°C (dec.) from CCl_4/pentane; NMR ($CDCl_3$): $\tau = 2.5$ (m, 5 aromatic H), 3.9 (t, 2 olefinic H), 4.6 (m, 2 tertiary H), 6.62 (t, 2 episulfide H)[10]]. No evidence has yet accrued for the formation of *(2)* and of thiepin[11] on thermolysis of *(1)*.



(1) *(6)* *(7)*

The thermal properties of *(1)* support the theoretically based prediction that *(2)* is not a 10π-aromatic compound.

Very recently, *Eggelte* and *Bickelhaupt*[12] have synthesized the obviously nonaromatic 1,4-dithiocin-6-yl acetate which fragments—*via* its hitherto undetected *syn*-benzene bisepisulfide valence tautomer—to phenyl acetate and sulfur.

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CAS Registry Numbers:
(1), 53111-69-6; *(3)*, 39078-08-5; *(4)*, 53111-70-9; *(5)*, 53111-71-0; *(7)*, 53111-72-1; 4-phenyl-1,2,4-triazoline-3,5-dione, 4233-33-4; *p*-toluenesulfonyl chloride, 98-59-9; thioacetic acid, 507-09-5

[1] *W. Schroth, F. Billig,* and *A. Zschunke,* Z. Chem. *9*, 184 (1969).

[2] *D. L. Coffen, Y. C. Poon,* and *M. L. Lee,* J. Amer. Chem. Soc. *93*, 4627 (1971).

[3] *A. T. Balaban* and *Z. Simon,* Rev. Roum. Chim. *10*, 1059 (1965).

[4] *B. A. Hess, Jr.* and *L. J. Schaad,* J. Amer. Chem. Soc. *95*, 3907 (1973).

[5] *E. Vogel, H.-J. Altenbach,* and *D. Cremer,* Angew. Chem. *84*, 983 (1972); Angew. Chem. internat. Edit. *11*, 935 (1972).

[6] *R. Schwesinger* and *H. Prinzbach,* Angew. Chem. *84*, 990 (1972); Angew. Chem. internat. Edit. *11*, 942 (1972).

[7] *H.-J. Altenbach* and *E. Vogel,* Angew. Chem. *84*, 985 (1972); Angew. Chem. internat. Edit. *11*, 937 (1972).

[8] *R. J. Abraham, H. Gottschalck, H. Paulsen,* and *W. A. Thomas,* J. Chem. Soc. *1965*, 6268.

[9] *K. Tori, T. Komeno,* and *T. Nakagawa,* J. Org. Chem. *29*, 1136 (1964).

[10] The NMR spectrum of *(7)* is completely analogous to that of the benzene oxide-4-phenyl-1,2,4-triazoline-3,5-dione adduct.

[11] Recently reported derivatives of thiepin permit no conclusions concerning the hitherto hypothetical thiepin-benzene episulfide equilibrium: *J. M. Hoffman, Jr.* and *R. H. Schlessinger,* J. Amer. Chem. Soc. *92*, 5263 (1970); *D. N. Reinhoudt* and *C. G. Kouwenhoven,* J. C. S. Chem. Comm. *1972*, 1233; Tetrahedron *30*, 2093 (1974).

[12] *H. J. Eggelte* and *F. Bickelhaupt,* Angew. Chem. *86*, 381 (1974); Angew. Chem. internat. Edit. *13*, 345 (1974).

A New Synthesis of Indolizines[**]

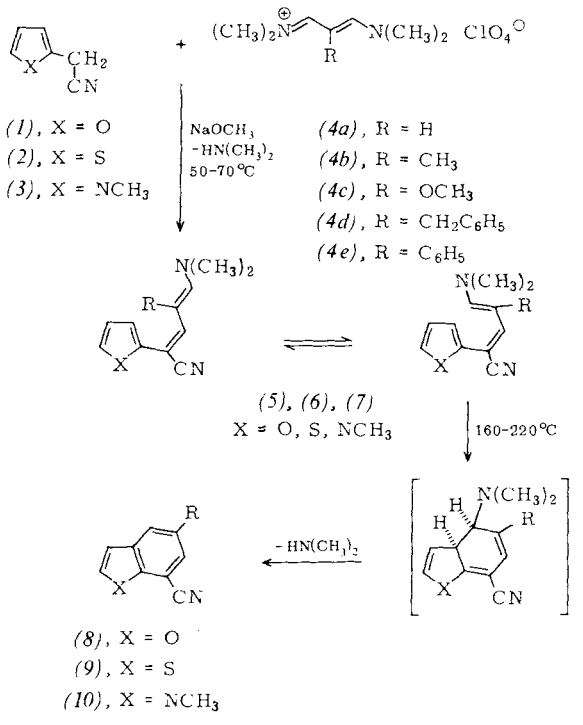
By *Christian Jutz, Rudolf M. Wagner,* and *Hans-G. Löbering*[*]

1,3,5-Hexatrienes bearing terminal dialkylamino groups undergo a 6π-electrocyclic reaction with elimination to form benzene derivatives. If a double bond of the hexatriene moiety is part of an aromatic π-system, then benzo-fused compounds are obtained[1-3].

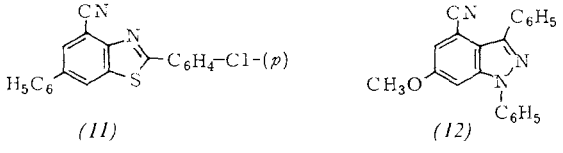
Benzo-annelation of furan, thiophene, and *N*-methylpyrrole can be accomplished particularly smoothly by thermolysis of the 5-dimethylamino-2-(2-hetaryl)-2,4-pentadienonitriles *(5)*, *(6)*, and *(7)*. At 160—220°C they cyclize with loss of

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dimethylamine to the 1-benzohetarene-7-carbonitriles *(8)*, *(9)*, and *(10)* (Table 1). The precursors *(5)*, *(6)*, and *(7)* are obtained in high yield by condensation of the hetarene-2-acetonitriles *(1)*, *(2)*, and *(3)* with the trimethinimium perchlorates *(4a)* to *(4e)* in pyridine or quinoline after addition of one equivalent of sodium methoxide and heating to 50—70 °C. Condensation and cyclization can also be performed to advantage in quinoline as a single vessel reaction without intermediate isolation. Determination of the dimethylamine eliminated affords a measure of the progress of the reaction. The steric effect of a substituent R on the rotamer equilibrium of *(5)*, *(6)*, and *(7)* can enhance the rate of cyclization or lower the temperature of thermolysis.



(11) *(12)*

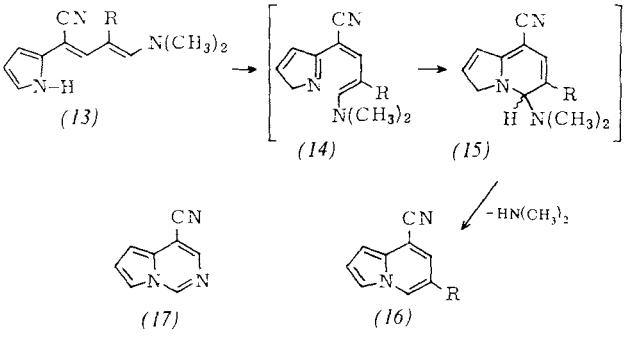
In like manner, 2-(4-chlorophenyl)thiazole-4-acetonitrile and *(4e)* afford 2-(4-chlorophenyl)-6-phenylbenzothiazole-4-carbonitrile *(11)* (98 %), m.p. 171—173 °C, while 1,3-diphenylpyrazole-4-acetonitrile and *(4c)* furnish 6-methoxy-1,3-diphenylindazole-4-carbonitrile *(12)* (84%), m.p. 151—158 °C.

Table 1. Examples of compounds of type *(8)*, *(9)*, *(10)*, and *(16)*. All compounds give correct elemental analyses and are substantiated by ^{1}H-NMR spectra.

Cpd.	R	Thermolysis conditions	Yield [%]	M.p. [°C]
(8a)	H	4 h, 200—220 °C	81 [a]	59
(8c)	OCH_3	2 h, 175—180 °C	93	103
(8d)	$CH_2C_6H_5$	1.5 h, 160—170 °C	82	73
(9a)	H	6 h, 200—220 °C	98 [a]	67 (67 [4])
(9c)	OCH_3	3 h, 180—190 °C	83	84—85
(9d)	$CH_2C_6H_5$	2 h, 170 °C	88	76—77
(10a)	H	6 h, 200—220 °C	94	68—69
(10b)	CH_3	1.5 h, 170 °C	85	87
(10c)	OCH_3	2 h, 170 °C	91	72—73
(10e)	C_6H_5	1 h, 160—170 °C	95	126
(16a)	H	3 h, 200—220 °C	80	74—75
(16c)	OCH_3	3 h, 180—185 °C	83	96—97
(16e)	C_6H_5	2 h, 170—180 °C	79	102—103

[a] Obtained from the isolated intermediates.

N-Unsubstituted pyrrole-2-acetonitrile also condenses like *(1)* to *(3)* with the salts *(4a)* to *(4e)* to form orange-yellow 5-dimethylamino-2-(2-pyrrolyl)-2,4-pentadienonitriles *(13a)* to *(13e)*. Contrary to our expectation, thermolysis does not lead to indole-7-carbonitriles, but exclusively to—characteristically lemon yellow—volatile indolizine-8-carbonitriles *(16a)* to *(16e)* (Table 1). The cyclization step must be accompanied by a [1.5]sigmatropic H migration *via* the two non-isolable intermediates *(14)* and *(15)*, if the postulate of an electrocyclic mechanism is to be upheld.



The hitherto unknown "6-azaindolizine", pyrrolo[1,2-*c*]pyrimidine-4-carbonitrile *(17)*, was prepared in analogous fashion by condensation and cyclization of pyrrole-2-acetonitrile with *N*,*N*-dimethyl-(3-dimethylamino-2-azaallylidene)ammonium perchlorate[5] in 55 % yield (yellow needles of m.p. 124 °C).

5-Dimethylamino-2-(2-pyrrolyl)-2,4-pentadienonitrile (13a)

Pyrrole-2-acetonitrile[6] (2.65 g, 25 mmol) and *(4a)* (5.70 g, 25 mmol) in anhydrous pyridine (20 ml) are reacted with an equivalent amount of $NaOCH_3$ in methanol (10 ml) and stirred for 2 h at 70 °C. After vacuum distillation of the pyridine, crystalline *(13a)* is rubbed with water, suction filtered, and chromatographed over alumina (activity III, basic) in CH_2Cl_2; 4.25 g (91 %) of yellow needles (from CH_2Cl_2/hexane), m.p. 147—148 °C.

Indolizine-8-carbonitrile (16a)

Compound *(13a)* (1.87 g, 10 mmol) in quinoline (3 ml) is heated to 200—220 °C for 3 h in a weak current of nitrogen (cessation of dimethylamine liberation); the contents of the flask are then rubbed with 50 ml of 1 N HCl, the precipitated *(16a)* dissolved in benzene, and the benzene solution subsequently washed once more with HCl and water. After sublimation of residue left on evaporation and chromatography on a small amount of alumina (activity III, neutral) one obtains 1.13 g (80%) of fine, lemon-yellow needles having a penetrating odor, m.p. 74—75 °C. ^{1}H-NMR (60 MHz, $CDCl_3$): $\tau = 1.92$ (dd, 1H^5, $J_{5,6} = 7.0$ Hz, $J_{5,7} = 1.0$ Hz); 2.56 (dd, 1H^1, $J_{1,2} = 2.8$ Hz, $J_{1,3} = 1.2$ Hz); 2.88 (dd, 1H^7, $J_{6,7} = 7.0$ Hz); 3.05 (dd, 1H^2, $J_{2,3} = 4.0$ Hz); 3.28 (dd, 1H^3); 3.50 (t, 1H^6). UV (CH_2Cl_2): λ_{max} (log ε) = 251 nm (4.51), 282 (sh, 3.32), 289 (3.49), 311 (3.46), 390 (3.32).

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(1), 2745-25-7; *(2)*, 20893-30-5; *(3)*· 24437-41-0; *(4a)*, 52950-92-2; *(4b)*, 53011-04-4; *(4c)*, 52950-94-4; *(4d)*, 52950-96-6; *(4e)*, 52950-98-8; *(5a)*, 52950-99-9; *(5c)*, 52950-00-5; *(5d)*, 52951-01-6; *(6a)*, 52951-02-7; *(6c)*, 52951-03-8; *(6d)*, 52951-04-9; *(7a)*, 52951-05-0; *(7b)*, 52951-06-1; *(7c)*, 52951-07-2; *(7e)*, 52951-08-3; *(8a)*, 52951-09-4; *(8c)*, 52951-10-7; *(8d)*, 52951-11-8; *(9a)*, 22780-71-8; *(9c)*, 52951-12-9; *(9d)*, 52951-13-0;

(10a), 52951-14-1; *(10b)*, 52951-15-2; *(10c)*, 52951-16-3; *(10e)*, 52951-17-4; *(11)*, 50781-59-4; *(12)*, 50781-54-9; *(13a)*, 52951-18-5; *(13c)*, 52951-19-6; *(13e)*, 52951-20-9; *(16a)*, 52951-21-0; *(16b)*, 52951-22-1; *(16e)*, 52951-23-2; *(17)*, 52951-24-3; 2-(4-chlorophenyl)thiazole-4-acetonitrile, 18832-93-4; 1,3-diphenylpyrazole-4-acetonitrile, 50781-53-8; pyrrole-2-acetonitrile, 50551-29-6; *N,N*-dimethyl-(3-dimethylamino-2-azaallylidene)ammonium perchlorate, 50781-48-1

[1] *Ch. Jutz, R. Kirchlechner*, and *H.-J. Seidel*, Chem. Ber. *102*, 2301 (1969).

[2] *Ch. Jutz* and *R. M. Wagner*, Angew. Chem. *84*, 299 (1972); Angew. Chem. internat. Edit. *11*, 315 (1972).

[3] *Ch. Jutz* and *E. Schweiger*, Chem. Ber. *107*, 2383 (1974).

[4] *P. Faller*, Bull. Soc. Chim. Fr. *1969*, 934.

[5] *H. Gold*, Angew. Chem. *72*, 956 (1960).

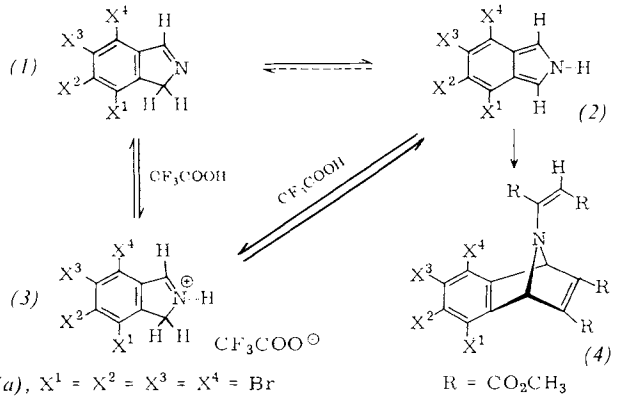
[6] *W. Herz, K. Dittmer*, and *S. J. Cristol*, J. Amer. Chem. Soc. *69*, 1699 (1947); *W. Herz, ibid. 75*, 483 (1953); *W. Herz* and *S. Tocker, ibid. 77*, 6354 (1955).

Stable Di- and Tetrabromo-2*H*-isoindoles[1]

By *Richard Kreher* and *Karl Josef Herd*[*]

Proof of the intermediary formation of the 1*H*-isoindole ("isoindolenine") *(1)*, X = H, has been obtained by independent synthesis, and of the existence of the tautomeric 2*H*-isoindole[3] *(2)*, X = H, by transformation reactions[4]. We have now concentrated our studies both on the fixation of the 1*H*- and 2*H*-isoindole structures by substituents on the heterocyclic system[1] and on their stabilization by halogen substituents on the carbocyclic system[2].

For the synthesis of the symmetrically substituted di- and tetrabromo-2*H*-isoindoles *(2a)*—*(2c)*, the relevant 1,2-bis-(bromomethyl)benzenes are converted by reaction with methanesulfonamide in basic solution into the readily isolable *N*-methanesulfonylisoindolines. Elimination of methanesulfinic acid is achieved with potassium *tert*-butoxide in dimethyl sulfoxide (1 h at room temperature) and leads *via* the intermediary 1*H*-isoindole *(1)* to the astonishingly thermostable 2*H*-isoindoles *(2)*, which are isolable in crystalline form and can be characterized by spectroscopical methods. According to the IR spectra ($\nu_{NH} \approx 3380$—$3420\,cm^{-1}$) and the ^{1}H-NMR spectra ($\tau_{CH} \approx 2.2$—2.9) the tautomeric equilibrium lies almost exclusively on the side of the 2*H*-isoindole form *(2)*, both in the solid state and in solution.



(a), $X^1 = X^2 = X^3 = X^4 = Br$
(b), $X^1 = X^4 = Br$, $X^2 = X^3 = H$
(c), $X^1 = X^4 = H$, $X^2 = X^3 = Br$
(d), $X^2 = X^3 = H$, $X^1 = OCH_3$, $X^4 = Br$

On reaction with trifluoroacetic acid, the 2*H*-isoindoles *(2a)*—*(2d)* are protonated in the α-position to give the 1*H*-isoindolium ions *(3)* whose formation clearly profits from the resonance stabilization of the benzenoid system and is thus energetically more favorable than the *N*-protonation. The reversibility of the *C*-protonation in acid medium (deuteriotrifluoroacetic acid) is detectable by complete H/D exchange in the pyrroloid system, whereas NH-deprotonation occurs in deuterium oxide/pentadeuteriopyridine. An exception is 5,6-dibromo-2*H*-isoindole *(2c)*, whose protonated form undergoes irreversible secondary reactions. Consequently, in contrast to the parent compound *(2)*, X = H, which spontaneously polymerize or polycondense in acid medium, the bromine-substituted 1*H*-isoindolium salts *(3)* generally have a spectroscopically detectable lifetime.

Table 1. 2*H*-Isoindoles *(2)* and 1*H*-isoindolium trifluoroacetates *(3)* [a].

(2a), Yield 72%, m.p. > 130 °C (decomp.) (ethyl acetate); ^{1}H-NMR (hexadeuterioacetone): $\tau = -3.0$ to -2.0 (s, broad, NH); 2.58 (d, $J = 3$ Hz, H^1, H^3); *(3a)*, ^{1}H-NMR (trifluoroacetic acid): $\tau = 0.72$ (t, $J = 2.5$ Hz, H^3); 4.70 (d, $J = 2.5$ Hz, $2H^1$)

(2b), Yield 86%, m.p. 55—56 °C (ether/petroleum ether, yield ≈40%); ^{1}H-NMR (hexadeuterioacetone): $\tau = -2.7$ to -1.1 (s, broad, NH); 2.58 (d, $J = 3$ Hz, H^1, H^3); 3.00 (s, H^5, H^6); *(3b)*, ^{1}H-NMR (trifluoroacetic acid): $\tau = 0.38$ (t, $J = 2.5$ Hz, H^3); 1.98 (d, $J = 8.5$ Hz, H^5 or H^6); 2.17 (d, $J = 8.5$ Hz, H^5 or H^6); 4.55 (d, $J = 2.5$ Hz, $2H^1$)

(2c), Yield 82%, m.p. > 120 °C (decomp.) (adsorptive filtration, yield 65%); ^{1}H-NMR (hexadeuterioacetone): $\tau = -3.0$ to -2.0 (s, broad, NH); 2.23 (s, H^4, H^7); 2.85 (d, $J = 3$ Hz, H^1, H^3); *(3c)*, ^{1}H-NMR (trifluoroacetic acid): $\tau = 0.47$ (t, $J = 2.5$ Hz, H^3); 1.3 to 2.5 (m, xH); 4.62 (d, $J = 2.5$ Hz, $2H^1$); 4.80 (m, xH), 5.2 to 5.6 (m, xH).

[a] The isolated isoindoles *(2a)* to *(2d)* give correct analyses and the expected molecular ions in the mass spectrum.

The deactivation of the *o*-quinonoid 10π-electron system of *(2)* is also apparent from the chemical behavior towards dienophiles. No Diels-Alder reaction is detectable on treatment with maleic anhydride under the usual conditions[5], whereas reaction with the more reactive dimethyl acetylenedicarboxylate leads to the 1 : 2 adducts *(4)*, whose formation is explained by 1,3-cycloaddition of the 2*H*-isoindoles *(2)* as well as by Michael addition of the NH group to the activated triple bond of the dienophile.

Table 2. 1 : 2-Adducts *(4)* of 2*H*-isoindoles *(2)*.

(4a), Yield 30%, m.p. 222 °C (methanol); ^{1}H-NMR ($CDCl_3$): $\tau = 4.47$ (s, 2 bridgehead H); 5.07 (s, 1 vinyl H); 6.18 (s, OCH_3); 6.22 (s, $2\,OCH_3$); 6.43 (s, OCH_3)

(4b), Yield 40%, m.p. 196—198 °C (methanol); ^{1}H-NMR ($CDCl_3$): $\tau = 2.92$ (s, 2 aromat. H); 4.35 (s, 2 bridgehead H); 4.94 (s, 1 vinyl H); 6.09 (s, OCH_3); 6.13 (s, $2\,OCH_3$); 6.35 (s, OCH_3)

(4d), Yield 49%, m.p. 191 °C; ^{1}H-NMR ($CDCl_3$): $\tau = 2.87$ (d, $J = 9$ Hz, 1 aromat. H); 3.43 (d, $J = 9$ Hz, 1 aromat. H); 4.27 (d, $J = 2.5$ Hz, 1 bridgehead H); 4.46 (d, $J = 2.5$ Hz, 1 bridgehead H); 4.98 (s, 1 vinyl H); 6.15 (s, OCH_3); 6.10 (s, OCH_3); 6.17 (s, $2\,OCH_3$); 6.37 (s, OCH_3).

In this case, the 5,6-dibromo-2*H*-isoindole *(2c)* also displays irregular behavior; 1,3-cycloaddition leads similarly to intermediary formation of the 1 : 2 adduct, which, however, isomerizes to tetramethyl 7,8-dibromo-3a,9b-dihydrobenzo[*g*]indole-2,3,3a,4-tetracarboxylate. Structurally analogous 1 : 2 adducts are formed on reaction of *N*-alkylisoindoles with the same dienophile[6, 7].

According to the above results, halogen atoms on the benzene ring effect a significant thermal stabilization of the heterocyclic 10π-electron system and a chemical deactivation toward electrophilic and dienophilic components. Reactivity studies[8]

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ought to clarify whether electronic effects or steric factors are primarily responsible for the two phenomena.

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(1a), 52964-16-6; *(1b)*, 52964-17-7; *(1c)*, 52964-18-8; *(1d)*, 52964-19-9; *(2a)*, 52964-20-2; *(2b)*, 52964-21-3; *(2c)*, 52964-22-4; *(2d)*, 52964-23-5; *(3a)*, 52964-24-6; *(3b)*, 52964-25-7; *(3c)*, 52964-26-8; *(4a)*, 53042-27-6; *(4b)*, 52964-27-9; *(4d)*, 52964-28-0; 1,2-bis(bromomethyl)-3,4,5,6-tetrabromobenzene, 53042-28-7; 1,2-bis(bromomethyl)-3,6-dibromobenzene, 52964-29-1; 1,2-bis(bromomethyl)-4,5-dibromobenzene, 6425-67-8; 1,2-bis(bromomethyl)-3-bromo-6-methoxybenzene, 52964-30-4; methanesulfonamide, 3144-09-0; 4,5,6,7-tetrabromo-*N*-methanesulfonylisoindoline, 52964-31-5; 4,7-dibromo-*N*-methanesulfonylisoindoline, 52964-32-6; 5,6-dibromo-*N*-methanesulfonylisoindoline, 52964-33-7; 4-bromo-7-methoxy-*N*-methanesulfonylisoindoline 52964-34-8; trifluoroacetic acid, 76-05-1; dimethyl acetylenedicarboxylate, 762-42-5

[1] Studies on the Chemistry of Isoindoles and Isoindolenines. Part 10.—This work was supported by the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft.—Part 9: [2].

[2] *R. Kreher* and *K. J. Herd*, Z. Naturforsch. *29b*, 683 (1974), in press.

[3] *R. Kreher* and *J. Seubert*, Z. Naturforsch. *20b*, 75 (1965); *R. Kreher*, Habilitationsschrift, Technische Hochschule Darmstadt 1967.

[4] For the isolation of the isoindole cf. *R. Bonnett* and *R. F. C. Brown*, J. C. S. Chem. Comm. *1972*, 393; *R. Bonnett*, *R. F. C. Brown*, and *R. G. Smith*, J. C. S. Perkin I *1973*, 1432; *J. Bornstein*, *D. E. Remy*, and *J. E. Shields*, J. C. S. Chem. Comm. *1972*, 1149; *G. M. Priestley* and *R. N. Warrener*, Tetrahedron Lett. *1972*, 4295.

[5] Review: *R. Livingstone* in Rodd's Chemistry of Carbon Compounds: Heterocyclic Compounds. 2nd Edit., Elsevier, Amsterdam 1973, Vol. IV A, p. 470ff.; *J. D. White* and *M. E. Mann*, Advan. Heterocycl. Chem. *10*, 113 (1969).

[6] *R. Kreher* and *J. Seubert*, Angew. Chem. 77, 1029 (1965); Angew. Chem. internat. Edit. *4*, 982 (1965).

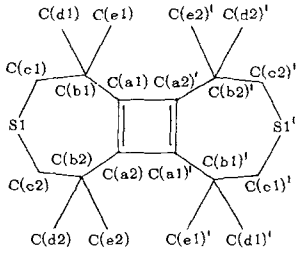
[7] *C. O. Bender*, *R. Bonnett*, and *R. G. Smith*, J. Chem. Soc. *C 1970*, 1251; *L. J. Kricka* and *J. M. Vernon*, J. C. S. Perkin I *1972*, 904; Chem. Commun. *1971*, 942.

[8] *R. Kreher*, Angew. Chem. *85*, 1061 (1973); Angew. Chem. internat. Edit. *12*, 1022 (1973).

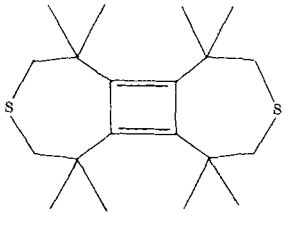
The Structure of a Rectangular Cyclobutadiene[**]

By *Hermann Irngartinger* and *Hans Rodewald*[*]

The geometry of the cyclobutadiene derivative 3,3,7,7,10,10,14,14-octamethyl-5,12-dithiatricyclo[7.5.0.0^{2,8}]-tetradeca-1(9),2(8)-diene *(1)*[1], whose isolation was first reported by *Kimling* and *Krebs*[2], has been established by X-ray structural analysis.



(1)



(2)

Intensity measurements were carried out on a single crystal[3] of *(1)*, which was sealed in a glass capillary under nitrogen. The yellow crystals decompose at 240 °C. The crystallographic data are: $a = 14.925(4)$, $b = 10.457(1)$, $c = 6.397(4)$ Å; $\alpha = 101.11(2)°$, $\beta = 103.77(4)°$, $\gamma = 90.86(2)°$; space group: $P\bar{1}$; $Z = 2$; $D_{calc.} = 1.18$ g cm^{-3}. A total of 4615 reflections (including 1504 that were regarded as unobserved) were measured by the balance filter method on a computer-controlled diffractometer using MoKα radiation. The structure could be solved by the heavy atom method. Refinement by the least-squares technique using anisotropic thermal parameters for the C and S atoms and isotropic thermal parameters for the H atoms yielded a conventional *R* factor of 0.044.

The unit cell contains two independent molecules the centers of which coincide with crystallographic centers of symmetry. The conformation and molecular parameters of the two independent halves of the molecule are almost indentical. Bond lengths and angles of chemically equivalent atoms were averaged (Fig. 1).

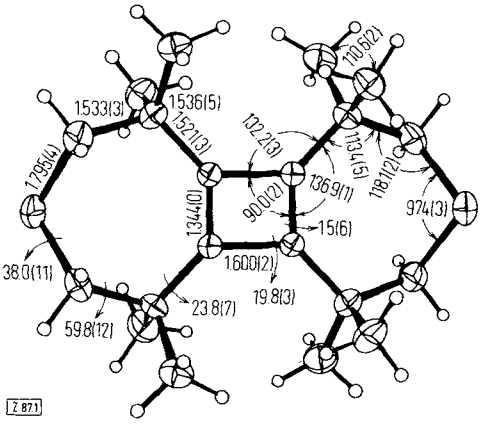


Fig. 1. Averaged bond lengths [Å] and angles [°] of *(1)* with the scatter of the last decimal place in brackets (standard deviation: 0.002 Å and 0.1° resp.). Values next to arrow heads refer to the mean absolute value of the torsional angle [°] [4].

In the crystal the four-membered ring of *(1)* clearly has a planar, rectangular structure, with sidelengths of 1.344 Å and 1.600 Å at an angle of 90°. The shorter bond is approximately the same length as a cyclobutene double bond (1.32—1.36 Å[5]).

The bonds of the four-membered ring which couple the seven-membered rings together are exceptionally longer than the C_{sp^2}—C_{sp^2} single bonds in 3,4-bis(methylene)cyclobutene (1.488 and 1.516 Å[6]). The elongation of these bonds in *(1)* (Fig. 2) might be due, in part, to the repulsive interactions of the methyl groups parallel to C(a)—C(a)'; elongations of 0.02—0.06 Å have been found for the corresponding bonds in aromatic five- and six-membered ring systems having two *tert*-butyl groups in the *ortho* position[7]. Hence, the structural formula *(1)* is favored over that of *(2)*. The results of an electron density difference calculation with $F_{obs.}$—$F_{calc.}$ indicate the presence of bent bonds in the four-membered ring.

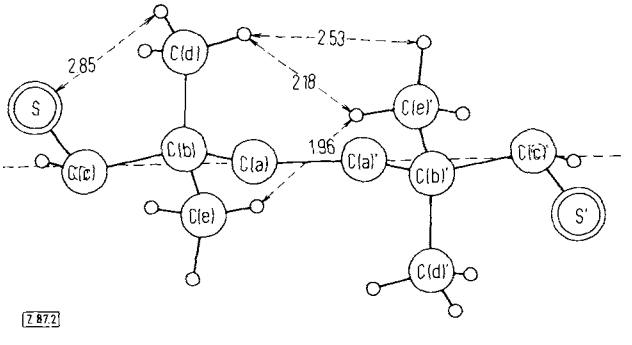


Fig. 2. Conformation of *(1)* viewed along the short edge of the cyclobutadiene. The H···H contacts (Å) are shown with broken lines.

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The C(b) atoms attached directly to the cyclobutadiene ring deviate by 0.19 Å from the plane of the ring, C(b1) and C(b2) being inclined in one direction and C(b1)' and C(b2)' in the opposite direction, thus resulting in a step-like conformation (see Fig. 2). The atoms C(b)—C(a)—C(a)—C(b) in a seven-membered ring lie almost in a plane inclined at about 10.6° to the plane of the cyclobutadiene ring. Transannular interaction between the MOs of the electrons in the lone pairs on sulfur and the π electrons of the C(a)=C(a) bond in the thiacycloheptene ring of *(1)* may be ruled out, since no similar interaction could be established[9] in 3,3,6,6-tetramethyl-1-thia-4-cycloheptyne, which has an analogous conformation with even shorter contacts ($S\cdots C_{sp}=2.94$ Å)[8].

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(1), 40219-42-9

[1] Review: *G. Maier*, Angew. Chem. 86, 491 (1974); Angew. Chem. internat. Edit. 13, 425 (1974).

[2] *H. Kimling* and *A. Krebs*, Angew. Chem. 84, 952 (1972); Angew. Chem. internat. Edit. 11, 932 (1972).

[3] We thank *G. Ranaldi* and Prof. *A. Krebs* for supplying us with the crystal.

[4] Figure 1 was obtained by means of the ORTEP program of *C. K. Johnson*, Report ORNL-3798, Oak Ridge National Laboratory, Oak Ridge, Tennessee (1965). The vibration ellipsoids of the C and S atoms are drawn at the 50% probability level; the radius of the H atoms was fixed at 0.08 Å.

[5] Summarized list: *D. Seebach* in Houben-Weyl: Methoden der Organischen Chemie, Thieme, Stuttgart 1971, Vol. IV/4, Tabelle 4.

[6] *A. Skancke*, Acta Chem. Scand. 22, 3239 (1968).

[7] *G. J. Visser* and *A. Vos*, Acta Crystallogr. B 27, 1802 (1971).

[8] *J. Haase* and *A. Krebs*, Z. Naturforsch. 27a, 624 (1972).

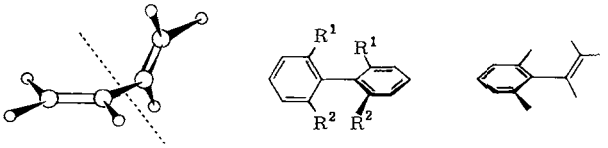
[9] *H. Schmidt, A. Schweig*, and *A. Krebs*, Tetrahedron Lett. 1974, 1471; *G. Lauer, C. Müller, K.-W. Schulte, A. Schweig*, and *A. Krebs*, Angew. Chem., in press.

Partial Enantiomerization of an Atropisomeric Butadiene[1]

By *Manfred Rösner* and *Gert Köbrich* (deceased)[*]

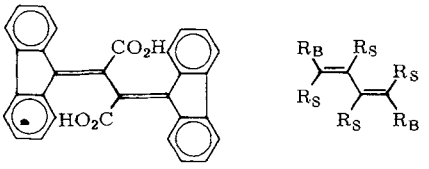
If formation of the *cisoid*- and *transoid*-coplanar conformations in butadienes is hindered by bulky substituents, occurrence of the atropisomers *(1)* is to be expected. The situation resembles that in the atropisomeric biphenyls *(2)*[3] and highly substituted styrenes *(3)*[4].

A characteristic difference exists between the symmetry of the biphenyl- *(2)* and butadiene systems *(1)*: owing to their dihedral symmetry, atropisomeric biphenyls require definite substitution patterns [*e.g.* $R^1 \neq R^2$ in *(2)*] in order to be chiral, and hence resolvable into optical enantiomers, whereas non-planar butadienes *(1)* belong to the point group C_2 or C_1 and are always chiral.



(1) *(2)* *(3)*

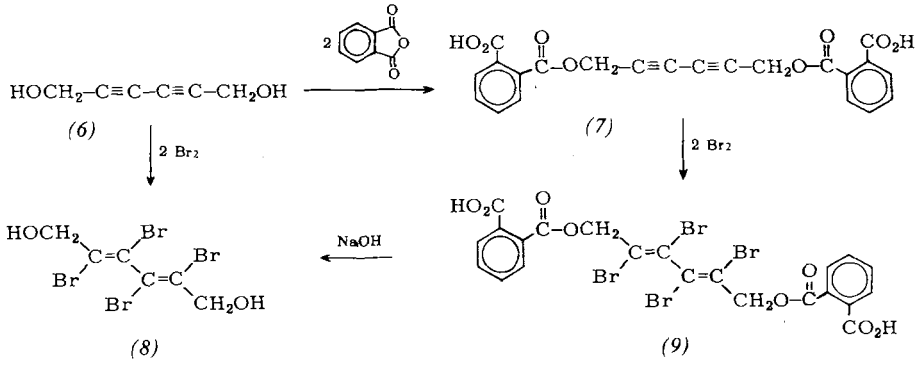
As early as 1957, *St. Goldschmidt et al.* succeeded in paving the way to partial enantiomerization of fulgenic acid *(4)*[5]; however, the enantiomers proved to be sterically very unstable (complete racemization in 22 min at 20 °C).



(4) *(5)*

The chirality of non-planar butadienes was conceptually introduced[6] in previous studies of this series and was demonstrated ^{1}H-NMR-spectroscopically on the basis of the anisochronism of prochiral substituents[6–8]. An independent demonstration of this chirality could recently be made by the signal splitting in the ^{1}H-NMR spectrum of certain butadienes in the presence of an optically active shift reagent[2]. The bulkiness of the four "blocking" substituents R_S in *(5)* *directly* hinder the coplanar orientation of the two double bonds. In addition, the two substituents R_B exert a buttressing effect in that they render a valence angle deformation of the groups R_S very difficult and thus *indirectly* hinder coplanar orientation of both halves of the molecule[7, 9].

We report here on the synthesis and partial resolution of the butadienes 2,3,4,5-tetrabromo-2,4-hexadiene-1,6-diol *(8)* and 2,2'-[2,3,4,5-tetrabromo-2,4-hexadienylenebis(oxycarbonyl)]dibenzoic acid *(9)*. 2,4-Hexadiyne-1,6-diol *(6)*, which is accessible in 90% yield by Glaser coupling of propargyl alcohol[10], was converted by reaction with 2 equivalents of phthalic anhydride in pyridine into the bis(phthalic half ester) *(7)* (yield 95%)[11], which, on bromination in acetone (initially at −45 °C, then at 0 °C) gave the tetrabromide *(9)* (colorless crystals; m.p. 177—178 °C, from chloroform) in 30 to 50% yield[12]. Reaction of *(9)* with 2 equivalents of D-(+)-α-phenylethylamine in acetone afforded a crystalline ammonium salt, whose diastereoisomers could be separated after several digestions with hot acetone.



(6) *(7)* *(8)* *(9)*

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There remained a product having a specific rotation of $[\alpha]_{546}^{20} = -9.5°$ (methanol), from which optically active (−)-*(9)* with $[\alpha]_{546}^{20} = -16.0°$ (in acetone) could be separated by treatment with dilute H_2SO_4. Treatment of (−)-*(9)* with dilute NaOH at room temperature afforded (−)-(*E*,*E*)-*(8)* with $[\alpha]_D^{20} = -14.3°$ (in acetone), which was identical (except for optical activity) with a product obtained by bromination of *(6)* (m.p. 100—101 °C, from chloroform)[13].

The optically active butadienes (−)-*(8)* and (−)-*(9)* are optically stable in the solid state; however, they gradually racemize in solution at room temperature. We have measured the kinetics of the racemization polarimetrically[14] and determined: for (−)-*(9)* [the values for (−)-*(8)* are given in brackets], an activation energy of $E_{exp} = 20.7 \pm 0.3$ kcal/mol (21.7 ± 0.3), $\Delta H^{\neq} = 20.1 \pm 0.3$ kcal/mol (21.1 ± 0.3), $\Delta S^{\neq} = -10.2 \pm 1.0$ cal mol^{-1} K^{-1} (−8.8 ± 1.0). This data provides a free enthalpy of activation $\Delta G^{\neq}$ (at 20 °C) of 23.1 ± 0.3 kcal/mol for (−)-*(9)* and 23.7 ± 0.3 kcal/mol for (−)-*(8)*.

From these results it would appear that stable enantiomers of chiral butadienes having *monoatomic* substituents R_S as blocking groups cannot exist in solution at room temperature (I can be ruled out as substituent because of the decomposability of the corresponding butadienes). We are at present attempting the synthesis of butadienes containing bulky *polyatomic* substituents R_S (*e.g. tert*-butyl). If the buttressing effect of the substituents R_B is sufficiently large[15], (*E*,*E*)-1,2,3,4-tetrabromobutadienes should also be able to form stable atropisomers in solution at room temperature.

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CAS Registry Numbers:
(6), 3031-68-3; *(7)*, 24996-68-7; (−)-*(8)*, 53152-83-3; (−)-*(9)*, 53111-74-3; phthalic anhydride, 85-44-9

[1] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Chiral Butadienes, Part 5.—Part 4: [2].

[2] *A. Mannschreck, V. Jonas, H.-O. Bödecker, H.-L. Elbe*, and *G. Köbrich*, Tetrahedron Lett. *1974*, 2153.

[3] *E. L. Eliel*: Stereochemie der Kohlenstoffverbindungen, Verlag Chemie, Weinheim 1966, p. 183; *S. F. Mason, R. H. Seal*, and *D. R. Roberts*, Tetrahedron *30*, 1671 (1974).

[4] *R. Adams* and *J. W. Mecorney*, J. Amer. Chem. Soc. *67*, 798 (1945); *C. S. C. Yang* and *R. S. H. Liu*, Tetrahedron Lett. *1973*, 4811.

[5] *St. Goldschmidt, R. Riedle*, and *A. Reichardt*, Liebigs Ann. Chem. *604*, 121 (1957).

[6] *G. Köbrich, A. Mannschreck, R. A. Misra, G. Rissmann, M. Rösner*, and *W. Zündorf*, Chem. Ber. *105*, 3794 (1972).

[7] *G. Köbrich, B. Kolb, A. Mannschreck*, and *R. A. Misra*, Chem. Ber. *106*, 1601 (1973).

[8] *H.-L. Elbe* and *G. Köbrich*, Chem. Ber. *107*, 1654 (1974).

[9] *H.-O. Bödecker, V. Jonas, B. Kolb, A. Mannschreck*, and *G. Köbrich*, Chem. Ber., in press.

[10] Following the procedure described by *A. S. Hay*, J. Org. Chem. *27*, 3320 (1962).

[11] Compound *(7)* had already been prepared *via* another route: *M. D. Cameron* and *G. E. Bennett*, J. Org. Chem. *22*, 557 (1957) (m.p. 145.5—147 °C); it gradually decomposes with violet discoloration (cf. *G. Wegner*, Z. Naturforsch. *24b*, 824 (1969)). The disodium salt is stable.

[12] The empirical formula of *(9)* is confirmed by elemental analysis and MS. ^{1}H-NMR (100 MHz, D_6-acetone): δ = 7.85 (m, 2H aromat.), 7.65 (m, 6H aromat.), 9—10 ppm (broad, 2OH); δ = 5.25 ppm (AB system, 2 × CH_2, $\delta_A - \delta_B = 5.3$ Hz, $J_{AB} = 13.5$ Hz).

[13] ^{1}H-NMR of *(8)* (100 MHz, D_6-DMSO): AB system at δ = 4.3 ppm with $\delta_A - \delta_B = 4.8$ Hz, $J_{AB} = 14$ Hz. Since the signals at 145 °C do not show any coalescence, the energy barrier to rotation about the central single bond of the butadiene system of *(8)* must be $\Delta G_c^{\neq} \geq 21.1$ kcal/mol; cf. Ref. [6, 7]. *(8)* has already been mentioned but not characterized: Jap. Pat. 7036428 and 7235409; Chem. Abstr. 75, P141752g (1971); 78, P4748h (1973).

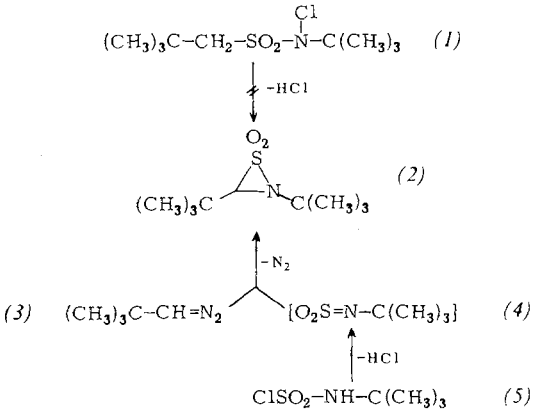
[14] Double determinations at 546 nm and 365 nm in each case at seven different temperatures between 15 and 47 °C [for (−)-*(9)*] and at five different temperatures between 20 and 47 °C [for (−)-*(8)*].

[15] For example, in the case of (*E*,*E*)-1,2,3,4-tetrachlorobutadiene a $(CH_3)_2COH$ group as R_B with 8.3 kcal/mol has more than double the buttressing effect than the CH_2OH (3.7 kcal/mol) or the CH_3OCH_2 group (4.0 kcal/mol) [2, 9].

2,3-Di-*tert*-butylthiaziridine 1,1-Dioxide[**]

By *Helmut Quast* and *Frieder Kees*[*]

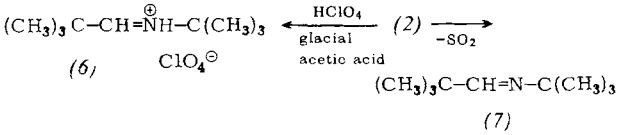
The first thiadiaziridines have recently been prepared in the form of their 1,1-dioxides[1, 2]. We have now synthesized the first thiaziridine 1,1-dioxide *(2)*. Thiaziridine 1,1-dioxides have formerly only occasionally been postulated as intermediates[3].



While 1,3 elimination of HCl was unsuccessful when attempted with the *N*-chlorosulfonamide *(1)*[5], which is readily accessible from neopentylsulfonyl chloride[4], we were able to apply the reaction of diazo compounds with sulfenes[6], which has proved of value in the preparation of thiirane 1,1-dioxides, to the *N*-sulfonylamine *(4)*[8] prepared *in situ* from *(5)*[7]. *(2)* crystallizes as colorless needles from pentane at −78 °C. Proof of structure rests on S analysis[10], the base equivalent, mass spectra[11], and reactions.

The molecular peak expected for $C_9H_{19}NO_2S$ could not even be detected in the 16 eV mass spectrum. Instead the spectrum merely shows products of thermal decomposition, *i.e. (7)* and SO_2. In contrast, determination of the base equivalent mass by titration with 0.1 N perchloric acid in glacial acetic acid was surprisingly straightforward[12]. A 91% yield of *(6)*[13] crystallized out.

Pyrolysis without solvent for 10 min at 60—80 °C gave 91 to 95% of SO_2 which was determined successively by gas volumetry and gravimetry[15]. In CCl_4 the SO_2 is accompanied by a quantitative amount of the azomethine *(7)*, as established by spectroscopic comparison (IR, NMR) with an authentic sample[14].



Following the formation of SO_2 in 2.5×10^{-4} M *n*-hexane solution by UV spectroscopy at 288.5 nm shows first-order

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[**] Three-Membered Heterocycles, Part 2.—Part 1: [2]. This work was supported by the Fonds der Chemischen Industrie. The results are taken from the planned Dissertation of *F. Kees*.

decomposition to occur over more than three half-lives with $k(25\,^{\circ}C) = (9.05 \pm 0.05) \times 10^{-5}\,s^{-1}$.

2,3-Di-tert-butylthiaziridine 1,1-dioxide (2)

A solution of *(5)*[7] (2.0 g, 11.7 mmol) in ether (30 ml) is added dropwise to a solution of *(3)*[9] (1.2 g, 12.2 mmol) and triethylamine (1.26 g, 12.5 mmol) in ether (50 ml) under N_2 at $-78\,^{\circ}C$ for 30 min. After 2 h at $-78\,^{\circ}C$ the reaction mixture is filtered, the ether distilled off *in vacuo* at $-50\,^{\circ}C$, and the residue sublimed at $0\,^{\circ}C/10^{-5}$ torr on to a finger cooled to $-60\,^{\circ}C$. Yield: 1.02 g (43%), dec. p. 40—43 °C. IR (CCl_4): no NH, 1325, 1177 cm^{-1} (SO_2).—^{1}H-NMR (CCl_4): $\delta = 1.03$ (s, tBu), 1.33 (s, tBu), 3.72 ppm (s, CH).—UV (*n*-hexane): Only end absorption above 200 nm[11].

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CAS Registry Numbers:
(2), 53111-73-2; *(3)*, 762-64-1; *(5)*, 33581-95-2

[1] a) *J. W. Timberlake* and *M. L. Hodges*, J. Amer. Chem. Soc. *95*, 634 (1973); b) *J. W. Timberlake, M. L. Hodges*, and *A. W. Garner*, Tetrahedron Lett. *1973*, 3843; c) *H.-H. Chang* and *B. Weinstein*, J. C. S. Chem. Comm. *1973*, 397.

[2] *H. Quast* and *F. Kees*, Tetrahedron Lett. *1973*, 1655.

[3] a) *B. Johnson* and *J. B. Douglass*, J. Amer. Chem. Soc. *63*, 1571 (1941); *F. G. Bordwell* and *G. D. Cooper*, *ibid.* *73*, 5187 (1951); *W. V. Farrar*, J. Chem. Soc. *1960*, 3058; b) *Note added in proof* (Oct. 15, 1974): Unsuccessful attempts at synthesis have meanwhile been reported: *J. C. Sheehan, U. Zoller*, and *D. Ben-Ishai*, J. Org. Chem. *39*, 1817 (1974).

[4] *H. Quast* and *F. Kees*, Synthesis *1974*, 489.

[5] *F. Kees*, Diplomarbeit, Universität Würzburg 1972.

[6] Survey: *N. H. Fischer*, Synthesis *1970*, 393.

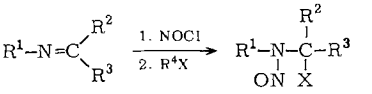
[7] *W. L. Matier, W. T. Comer*, and *D. Deitchman*, J. Med. Chem. *15*, 538 (1972).

[8] Regarding the chemistry of the *N*-sulfonylamines see: *B. Weinstein* and *H. H. Chang*, Tetrahedron Lett. *1974*, 901, and references cited therein.

Synthesis of α-Functional Nitrosamines

By *Manfred Wiessler*[*]

Addition of nitrosyl chloride to olefins leads to vicinal chloro nitroso compounds or their dimers[11]. If the reaction proceeds in the same manner, the addition of nitrosyl chloride to Schiff bases[2] could lead to α-chloro *N*-nitroso compounds— ideal intermediates for the synthesis of α-functional nitrosamines. In this context, particular interest attaches to the synthesis of α-hydroxy nitrosamines or their esters for they are of special significance for the elucidation of the metabolism of nitrosamines and for studying the carcinogenic action of this class of compounds. The present communication briefly reports the addition of nitrosyl chloride to Schiff bases.



(1)-(5) *(6)-(10)*

(a), X = CH_3O; *(b)*, X = CH_3CO_2;
(c), X = p-NO_2-$C_6H_4CO_2$; *(d)*, X = Cl

If the Schiff base *(1)*[3] is reacted at $-30\,^{\circ}C$ with the stoichiometric amount of NOCl, rapid decoloration occurs. After addition of $CH_3OH/(C_2H_5)_3N$, $CH_3CO_2H/(C_2H_5)_3N$, or p-NO_2—$C_6H_4CO_2H/(C_2H_5)_3N$ at the same temperature and subsequent work-up, the compound *(6a)*, *(6b)*, or *(6c)* can be isolated. All the compounds of type *(7)*—*(10)* listed in Table 1 could be synthesized in the same way. Their structures are confirmed by analytical and spectroscopic data.

In an attempt to prepare compound *(9a)* only the starting materials were isolated. The methyl ether was apparently formed at $-30\,^{\circ}C$ but liberated methyl nitrite with regeneration of the double bond during work-up. The isolation of *(10a)* demonstrates the feasibility of preparing tertiary methyl ethers.

Table 1. α-Functional *N*-nitrosamines of type *(6)*—*(10)* prepared.

Reactant	Product	R^1	R^2	R^3	X	M.p. [°C] B.p. [°C/torr]	Yield [%]
(1)	*(6a)*	$(CH_3)_3C$	H	H	CH_3O	52/0.05	35
(1)	*(6b)*	$(CH_3)_3C$	H	H	CH_3CO_2	58/0.05	45
(1)	*(6c)*	$(CH_3)_3C$	H	H	p-NO_2—$C_6H_4CO_2$	113—114	50
(2)	*(7a)*	n-C_3H_7	H	C_2H_5	CH_3O	34/0.2	40
(2)	*(7b)*	n-C_3H_7	H	C_2H_5	CH_3CO_2	[a]	25
(2)	*(7c)*	n-C_3H_7	H	C_2H_5	p-NO_2—$C_6H_4CO_2$	oil	25
(3)	*(8a)*	—$(CH_2)_4$—		H	CH_3O	52/0.2	30
(3)	*(8b)*	—$(CH_2)_4$—		H	CH_3CO_2	[a]	20
(4)	*(9a)*	CH_3	H	C_6H_5	CH_3O	[b]	—
(4)	*(9b)*	CH_3	H	C_6H_5	CH_3CO_2	[c]	30
(4)	*(9c)*	CH_3	H	C_6H_5	p-NO_2—$C_6H_4CO_2$	115—116	40
(5)	*(10a)*	n-C_3H_7	CH_3	CH_3	CH_3O	[c]	30

[a] Molecular distillation.
[b] See text.
[c] Not distilled.

It may be assumed that the chlorides *(6d)*—*(10d)* are formed on addition of NOCl to the Schiff bases *(1)*—*(5)*. Confirmation of this course is provided by the isolation of *(6d)* [NMR ($CDCl_3$): $\tau = 4.90$ (2H, s), 8.35 (9H, s)]. The chloride decomposes already at room temperature. Since the secondary chlorides should be even more reactive we have not attempted to isolate them. So far, *N*-chloromethyl-*N*-nitrosomethyl-

[9] *G. M. Kaufmann, J. A. Smith, G. G. Van der Stouw*, and *H. Shechter*, J. Amer. Chem. Soc. *87*, 935 (1965).

[10] The ready decomposition precludes C, H, N analysis.

[11] Cf. the spectroscopic data for 2,3-di-*tert*-butylthiirane 1,1-dioxide [5] [IR (CCl_4): 1315, 1162 cm^{-1} (SO_2), ^{1}H-NMR (CCl_4): $\delta = 1.13$ (s, tBu), 2.90 ppm (s, CH)] and 2,3-di-*tert*-butylthiadiaziridine 1,1-dioxide [1a, 1c].

[12] *W. Huber*: Titrations in Nonaqueous Solvents. Academic Press, New York 1967.

[13] Identified by comparison with the authentic compound prepared from *(7)* [14] and perchloric acid.

[14] *R. Bonnett*, J. Chem. Soc. *1965*, 2313; *J. C. Sheehan* and *J. H. Beeson*, J. Amer. Chem. Soc. *89*, 362 (1967).

[15] Apparatus: *H. Quast* and *E. Schmitt*, Liebigs Ann. Chem. *732*, 43 (1970).

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amine, which is also accessible *via* another route, is the only representative of this class of compounds that is stable at room temperature[4].

This method supplements and extends *Eiter*'s synthesis[5] of α-alkoxy nitrosamines. Compounds *(6a)*, *(7a)*, and *(8a)* can also be prepared in low yields by *Eiter*'s method but the impurities cannot be removed[6].

N-tert-Butyl-N-nitrosaminomethyl acetate (6b)

N-Methylene-*tert*-butylamine *(1)* (25 mmol) in CH_2Cl_2 is added dropwise to a 1 M NOCl solution in CH_2Cl_2 (25 ml) at −30 °C. After 10 min, a solution of triethylammonium acetate (25 mmol) in CH_2Cl_2 (20 ml) is added dropwise at the same temperature. The cold bath is removed. After the solution has warmed to room temperature it is shaken several times with water, the organic phase then being dried over Na_2SO_4, concentrated, and distilled. *(6b)*, b.p. 58 °C/0.05 torr, yield 2.05 g (45 %); NMR ($CDCl_3$): τ = 4.55 (2H, s), 7.95 (3H, s), 8.35 (9H, s); IR (CH_2Cl_2): 1755, 1480 cm^{-1}; UV (diethyl ether): $\lambda_{max} = 232$ nm (ε = 5700).

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CAS Registry Numbers:
(1), 13987-61-6; *(2)*, 7707-70-2; *(3)*, 505-18-0; *(4)*, 622-29-7; *(5)*, 22023-64-9; *(6a)*, 53198-37-1; *(6b)*, 53198-38-2; *(6c)*, 53198-39-3; *(6d)*, 53198-40-6; *(7a)*, 53230-00-5; *(7b)*, 53198-41-7; *(7c)*, 53198-42-8; *(8a)*, 53198-43-9; *(8b)*, 53198-44-0; *(9a)*, 53198-45-1; *(9b)*, 53198-46-2; *(9c)*, 53198-47-3; *(10a)*, 53198-48-4; $CH_3OH/(C_2H_5)_3N$, 10510-76-6; $CH_3CO_2H/(C_2H_5)_3N$, 5204-74-0; *p*-NO_2—$C_6H_4CO_2H/(C_2H_5)_3N$, 51694-06-5; NOCl, 2696-92-6.

[1] *L. J. Beckham, W. A. Fessler*, and *M. A. Kise*, Chem. Rev. *48*, 319 (1951); *R. Stroh* in Houben-Weyl: Methoden der organischen Chemie. Thieme, Stuttgart 1962, Vol. V/3, p. 934.

[2] *J. Turean*, Bull. Soc. Chim. Fr. *52*, 627 (1935).

[3] According to Houben-Weyl (Methoden der Organischen Chemie. Thieme, Stuttgart 1958, Vol. XI/2, p. 78), this azomethine is present; however, spectroscopic data indicate that it is better formulated as perhydro-1,3,5-triazine.

[4] *L. Keefer*, Tetrahedron Lett., in press; *M. Wiessler, ibid.*, in press.

[5] *K. Eiter, K. F. Hebenbrock*, and *H. J. Kabbe*, Liebigs Ann. Chem. *765*, 55 (1972).

[6] *M. Wiessler*, unpublished experiments.

The First Oxoniobate(III): $LiNbO_2$[1]

By *Gerd Meyer* and *Rudolf Hoppe*[*]

During attempts to prepare $Li_4Nb_3^{IV}O_8$, whose existence appears to be inadequately substantiated[2], we unexpectedly obtained inhomogeneous wine-red reaction products [$2Li_2O + 3NbO_2$; 900 °C, 35 d, small nickel bomb, under argon]. Apart from *hexagonal platelets* having a *bluish-black* luster (garnet red when viewed by transmitted light) the reaction mixture contained $LiNbO_3$[3] and some Li_3NbO_4[4], which are both colorless.

The same substance was obtained almost pure as a black powder (streak: wine-red) from corresponding mixtures of $Li_2O + NbO + NbO_2$ [700 °C, 3 d, small nickel bomb, under argon]. Debye-Scherrer powder photographs show the single crystals to be identical with the powder, which also contained a little $LiNbO_3$.

The Nb content [70.4 % (exp.); calc. 70.4$_6$ % ($LiNbO_2$), 60.0$_2$ (Li_2NbO_3), and 64.1$_5$ % ($Li_4Nb_3O_8$), respectively] and the increase in weight on careful oxidation [O_2, 700 °C, 12 h: Δ = +11.3 % (exp.); calc. +12.1$_4$ ($LiNbO_2$), +5.1$_7$ (Li_2NbO_3), and +5.5$_2$ % ($Li_4Nb_3O_8$)] as well as structural determination confirm the presence of $LiNbO_2$.

Rotating crystal (above [10.0]), Weissenberg (0*k.l*—2*k.l*), and precession diagrams (*hk*.0, *hk*.1 and *h*0.*l* and *h*1.*l*) indicate a hexagonal unit cell having $a = 2.90_5$ Å, $c = 10.46$ Å, $c/a = 3.60$; $Z = 2$.

Structural determination [128 0*k.l*—2*k.l*, I_0 data recorded with a two-circle diffractometer (Stadi 2 manufactured by Stoe, Darmstadt), $Mo_{K\alpha}$ radiation] ruled out the space groups $P6_3mc$ and $P\bar{6}2c$, which were also compatible with the extinctions, and confirmed the space group $P6_3/mmc$. Interpretation of the Patterson synthesis followed by Fourier difference syntheses and subsequent least-squares refinement led to the parameters listed in Table 1; $R = R' = 5.2_3$ %.

Table 1. Atomic parameters for $LiNbO_2$ (standard deviations in units of the last decimal place are given in parentheses).

Particle	Equiv. posn.	*x*	*y*	*z*	*B* [Å^2]
Li	2a	0	0	0	1.4(7)
Nb	2d	$0.\bar{6}$	$0.\bar{3}$	0.25	0.33(2)
O	4f	$0.\bar{3}$	$0.\bar{6}$	0.1263(4)	0.13(11)

According to these results the compound has a "filled" layer structure of MoS_2 type, which also occurs in NbS_2[5]. Nb^{3+} is in a trigonal-prismatic environment of 6 O^{2-} (distance 2.11$_8$ Å, 6×), which is surprising in view of its "diagonal relationship" to Ti^{2+}. Li^+ occupies octahedral sites between the NbO_2 layers (Li—O = 2.13$_5$ Å, 6×). The I_0 data discount any occupation of the corresponding tetrahedral sites, as shown by *R* values and especially *B* values resulting from test calculations.

Between 3 and 300 K $LiNbO_2$ exhibits temperature-independent magnetism with marked dependence upon field strength, and resembles NbO_2[6] to such a degree that, as with VO_2, it is presumably antiferromagnetic[7] (with $T_N > 300$ K).

The agreement between the Madelung part of the lattice energy

Table 2. Madelung part of the lattice energy (MAPLE) of $LiNbO_2$ [kcal/mol].

	from	binary	×		ternary	Δ	ΣΔ
Li^+	Li_2O	146.2	1	146.2	215.1	+ 68.9	+68.9
Nb^{3+}	NbO	1067.0	0.5	533.5	985.7	− 81.3	−40.7
Nb^{3+}	α′-NbO_2	1112.2	0.5	556.1		−126.5	−63.3
O^{2-}	Li_2O	543.5	0.5	271.8	543.5	0	0
O^{2-}	NbO	474.2	0.75	355.7	(2×)	+ 69.3	+51.9
O^{2-}	α′-NbO_2	575.9	0.75	431.9		− 32.4	−24.3
				Σ: 2295.2	2287.8		− 7.5 (0.3 %)

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(MAPLE[8]) of $LiNbO_2$ with the sum for corresponding binary oxides (cf. Table 2) is very good.

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$LiNbO_2$, 53320-08-4

[1] Part of the Dissertation by *G. Meyer*, Universität Giessen D 26. The present work was supported by the Deutsche Forschungsgemeinschaft and Farbwerke Hoechst AG.

[2] *D. E. Fornwalt*, U. S. At. Energy Comm., *TIM-696*, 7 (1961).

[3] *P. Bailey*, Thesis. Bristol 1952, cited by *H. D. Megaw*, Acta Crystallogr. 7, 187 (1954).

[4] *G. Blasse*, Z. Anorg. Allg. Chem. *326*, 44 (1963).

[5] *F. Jellinek*, Ark. Kemi *20*, 447 (1963).

[6] *G. Meyer* and *R. Hoppe*, to be published.

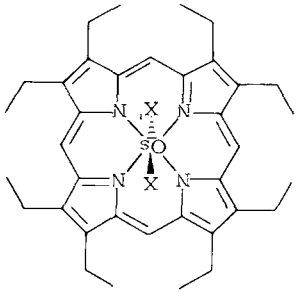
[7] *W. Rüdorff, G. Walter*, and *J. Stadler*, Z. Anorg. Allg. Chem. *297*, 1 (1958).

[8] *R. Hoppe*, Angew. Chem. *78*, 52 (1966); *82*, 7 (1970); Angew. Chem. internat. Edit. *5*, 95 (1966); *9*, 25 (1970); Advan. Fluorine Chem. *6*, 387 (1970).

Dinitrogen(octaethylporphinato)tetrahydrofuranosmium(II): A Nitrogen-Carrying Metalloporphyrin[**]

By *Johann Walter Buchler* and *Paul David Smith*[*]

Iron(II) porphins are known to bind a variety of small molecules, *e.g.* O_2, CO, NO, CH_3NC[1], but hitherto only a single dinitrogen complex, namely dinitrogen(protoporphyrin IX-diethylesterato)pyridineiron(II), has been mentioned[2]. The formation and chemical behavior of this compound as known to the authors[3] are quite amazing in view of well-accepted experience pertinent to the coordination chemistry of dinitrogen complexes. Therefore, the preparation and chemical characterization of other porphinatometal dinitrogen complexes is of interest inasmuch as hemoglobin effects O_2 uptake from N_2-containing air. The previously reported carbonyl(octaethylporphinato)tetrahydrofuranosmium(II) *(1)*[4] has a relatively low IR stretching frequency for the coordinated carbonyl group ($\tilde{\nu} = 1897\,cm^{-1}$). It was therefore expected from a rule expressed by *Chatt*[5] that the isosteric dinitrogen complex should exist.



Cpd.	Os"	X	X'
(1)	Os^{II}	CO	THF
(2)	Os^{VI}	O	O
(3)	Os^{II}	N_2	THF
(4)	Os^{IV}	OCH_3	OCH_3
(5)	Os^{II}	py	py
(6)	Os^{II}	THF	THF

When a drop of hydrazine hydrate is added to a solution of 0.13 mmol octaethylporphinatodioxoosmium(VI) *(2)*[6] in 20 ml tetrahydrofuran (THF) refluxing under N_2, the color of the solution changes within a minute from olive-green to red-violet (λ_{max} 525, 495, and 391 nm). After cooling and removing the volatile components under vacuum at 20 °C a crystalline dark violet residue is obtained. According to its IR spectrum [$\nu(N_2) = 2030\,cm^{-1}$; Fig. 1] and elemental analysis, this substance represents the desired dinitrogen(octaethylporphinato)tetrahydrofuranosmium(II) *(3)*. Like $[Os(NH_3)_5N_2]Br_2$ [$\nu(N_2) = 2028\,cm^{-1}$][7], *(3)* can be kept in air for some time, but is thermolabile and very air-sensitive in solution.

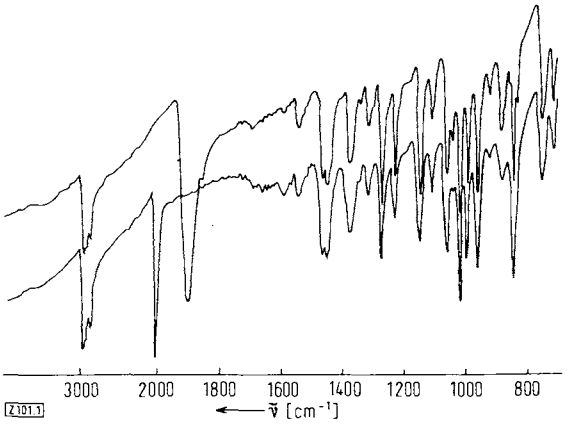


Fig. 1: Comparison of the IR spectra of carbonyl- *(1)* and dinitrogen-(octaethylporphinato)tetrahydrofuranosmium(II) *(3)* (lower trace); Perkin-Elmer 157, KBr.

N_2 and THF are liberated from *(3)* on heating to temperatures between 50 and 180 °C. This is evident from thermogravimetric[8] and IR spectroscopic investigation of the remaining solid as well as from mass spectrometric and vapor-phase chromatographic analysis of the gas phase liberated.

In THF solution at 20 °C, *(3)* shows the following reactions: 1. Autoxidation largely affords *(2)*; in the presence of CH_3OH the methoxide *(4)*[6] is formed.—2. Bubbling CO through the solution yields the carbonyl complex *(1)*.—3. Addition of pyridine furnishes the complex *(5)*[6] by replacement of the THF- and the N_2-ligand; however, in *(1)* at 20 °C only the THF ligand is substituted by pyridine[4].

When the dioxo complex *(2)* is reduced with diisobutylaluminum hydride in THF under argon, a red solution ($\lambda_{max} \approx 510$ nm), presumably containing *(6)*, is obtained. Under N_2, *(6)* is slowly transformed to *(3)*. *(3)* may react in this solution in the same manner as in the above mentioned reactions to give *(1)*, *(4)* or *(5)*.

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German version: Angew. Chem. 86, 820 (1974)

CAS Registry Numbers:
(1), 52649-89-5; *(2)*, 51349-77-0; *(3)*, 53352-71-9; *(4)*, 53352-69-5; *(5)*, 51286-87-4; *(6)*, 53352-72-0

[1] *E. Antonini* and *M. Brunori*: Hemoglobin and myoglobin in their reaction with ligands. North Holland, Amsterdam 1971.

[2] *S. McCoy* and *W. S. Caughey*, Biochemistry 9, 2387 (1970).

[3] *W. S. Caughey*, personal communication.—We thank Professor *Caughey* for the communication of unpublished results.

[4] *J. W. Buchler* and *K. Rohbock*, J. Organometal. Chem. *65*, 223 (1974).

[5] *J. Chatt, J. R. Dilworth*, and *G. J. Leigh*, Chem. Commun. *1969*, 687.

[6] *J. W. Buchler* and *P. D. Smith*, Angew. Chem. *86*, 378 (1974); Angew. Chem. internat. Edit. *13*, 341 (1974).

[7] *A. D. Allen* and *J. R. Stevens*, Chem. Commun. *1967*, 1147.

[8] We thank BASF (Hauptlaboratorium), Ludwigshafen, for the thermogravimetric analysis.

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[**] This work was supported by the Deutsche Forschungsgemeinschaft.

Erratum

In the fifth line of the communication "Trialkoxycyclopropenylium Ions" by *Eckehard V. Dehmlow*, Volume 13, page 209, March 1974, the following correction should be made: "pyrolysis" should read "photolysis".

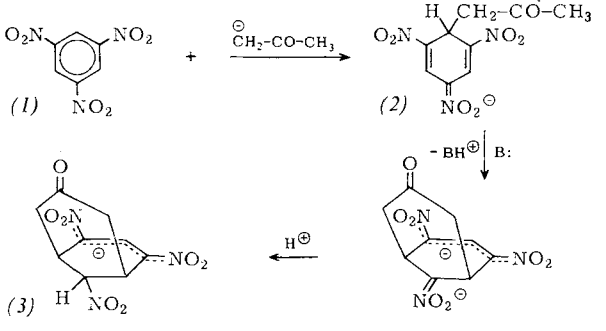
Reviews

Abstracts of selected progress reports and review articles

The aggregation of dissolved alkane chain molecules is reported on by *G. W. Brady*. X-ray scattering measurements on 1-iodoalkanes showed that spherical aggregates are formed in decalin as solvent. This is not the case in solvents with alkyl chains. Special attention is paid to the aggregation in decalin solutions which contain mixtures of molecules having chain lengths of C_m and C_n where $m+n=22$. The molecules arrange themselves in spherical formation with the iodine atoms on the outside and the alkyl chains on the inside. In mixtures containing molecules with shorter chains the iodine atoms also occupy positions at the periphery of the aggregate. [On the Aggregation of Dissolved Alkane Chain Molecules. Accounts. Chem. Res. 7, 174—180 (1974); 17 references]

[Rd 727 IE—L]

Anionic σ-complexes *(2)* have been studied by *M. J. Strauss*. The complexes are formed by addition of carbanions to electron-deficient arenes *(1)*; multiple additions have also been observed. Cyclizations with *meta* bridging may be regarded as intramolecular analogs of this reaction which, in the pres-



ence of bases (B:) lead, *e.g.*, to the bicycle *(3)*. [Carbanion Additions and Cyclizations Involving Anionic σ Complexes. Meta Bridging Reactions of Aromatics. Accounts Chem. Res. 7, 181—188 (1974); 63 references]

[Rd 728 IE—L]

Stable homoleptic alkylmetal compounds are reviewed in an article by *P. J. Davidson, M. F. Lappert*, and *R. Pearce*. "Homoleptic" compounds are those in which the metal is bonded only to ligands of the same type, *e.g.* $Ti(CH_3)_4$[$(CH_3)_3TiCl$, on the other hand, is referred to as "heteroleptic"]. The authors concern themselves especially with compounds of Si, Ge, Sn, Pb, Sc, Y, Ti, Zr, Hf, V, Cr, Mo, W, Cu, Zn, and Hg with bulky ligands which have no β hydrogen atom, such as *e.g.* $(CH_3)_3SiCH_2$, $[(CH_3)_3Si]_2CH$, $(CH_3)_3CCH_2$, and $(CH_3)_3SnCH_2$. The article contains a tabulated set of data on the synthesis, structure, bonding, and decomposition of several examples. [Stable Homoleptic Metal Alkyls. Accounts Chem. Res. 7, 209—217 (1974); 67 references]

[Rd 729 IE—L]

8α-Substituted flavins of biological importance are described in an article by *T. P. Singer* and *D. E. Edmondson*. Covalently bound flavin has been detected in a series of enzymes. The reactive 8α-methyl group of the isoalloxazine system in these enzymes is coupled with an amino acid side chain, either of histidine or of cysteine. The article deals with the methods for localization of the bond between amino acid residue and flavin, with the change in spectra and redox potentials of the flavin peptides relative to those of the free flavins, and with the chemical properties of histidyl- and cysteinylflavins. According to the results obtained so far, the amino acid sequence distant from the flavin residue also appear to influence the physicochemical properties of the flavin peptide. [8α-Substituted Flavins of Biological Importance. FEBS Lett. *42*, 1—14 (1974); 67 references]

[Rd 731 IE—R]

The regulation of iron absorption, which is discussed by *D. van Campen*, is still an essentially unknown process. It is known that a series of factors influence the absorption of iron, presumably *via* a primary control process that takes place at the cells of the mucous membrane of the small intestine. It is still unknown, however, how the cells receive information about the amounts of iron present. Transmission by humoral factors circulating in the blood and characterization of the cells during their formation are discussed as transfer mechanisms. [Regulation of Iron Absorption. Fed. Proc. *33*, 100—105 (1974); 67 references]

[Rd 732 IE—R]

The biochemical properties of microtubules are reviewed by *J. Bryan*. These cell organelles of the eukaryotes, whose main function, along with microfilaments, is motion in its broadest sense, contain tubulin, a globular protein. This consists of two chemically different protomers, the α- and β-tubulins. During evolution, both protomers have remained remarkably conservative in their chemical composition and, consequently, in their physical properties. This may be due to steric requirements. From the αβ-heterodimers a structure of higher order can be built which can serve as model for the microtubules. [Biochemical Properties of Microtubules. Fed. Proc. *33*, 152—157 (1974); 77 references]

[Rd 733 IE—R]

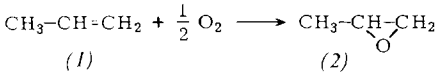
The interaction of drugs with microtubule proteins is discussed by *L. Wilson, J. R. Bamburg, S. B. Mizel, L. M. Grisham*, and *K. M. Creswell*. The main theme of the article centers on the reaction between tubulin, the protein of the microtubules and the receptors of several "spindle poisons", and the mitosis inhibitor colchicin. The binding of this inhibitor to the protein hinders polymerization of tubulin and thus leads to destruction of the microtubulus structure. Other substances such as the Vinca alkaloids or griseofulvin, bind to other sites of tubulin or inhibit mitosis *via* other mechanisms. [Interaction of Drugs with Microtubule Proteins. Fed. Proc. *33*, 158—166 (1974); 34 references]

[Rd 734 IE—R]

Patents

Abstracts of selected "Deutsche Offenlegungsschriften" (DOS), *i. e.* provisionally published specifications as filed with the German Patent Office

Propylene oxide *(2)* can be obtained with 90% selectivity by the aerial oxidation of propylene *(1)* on a rare-earth cata-

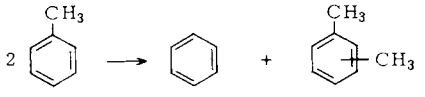


(1) *(2)*

lyst. The reaction takes place in the liquid phase at 150—170 °C and 50 bar. [DOS 2313023; Ordena Lenina Institut Khimicheskoi Fiziki Akademii Nauk USSR, Moscow (USSR)]

[PR 220 IE—G]

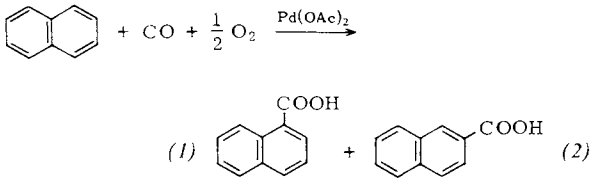
Benzene can be obtained in good yield in addition to xylene by the catalytic disproportionation of toluene in a current of hydrogen at 300—430 °C and 20—70 bar with residence



times of less than 20 s. The catalyst consists of a metal of the 8th transition group (Co, Ni) and an acidic aluminosilicate prepared from mordenite. [DOS 2345395; Texaco Development Corp., New York (USA)]

[PR 221 IE—G]

Aromatic carboxylic acids such as naphthalenecarboxylic acids *(1)* and *(2)* can be prepared from aromatic hydrocarbons, carbon monoxide, and oxygen in the presence of palladium

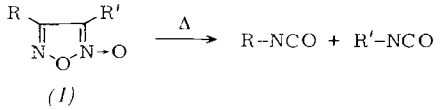


(1) *(2)*

acetate catalyst. The reaction takes place at temperatures of around 100 °C and pressures of around 10 bars in the liquid phase (Ac = $COCH_3$). [DOS 2340592; Teijin Ltd., Osaka (Japan)]

[PR 222 IE—G]

Thermal decomposition of furoxanes *(1)* in which the substituents R and R′ contain aliphatic carbons adjoining the carbon



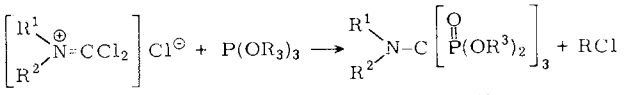
(1)

R, R′ = (subst.) alkyl; R–R′ = alkylene

atoms of the furoxane ring leads to isocyanates. The process makes it possible to prepare alkylene diisocyanates starting from cycloolefins *via* the stages of pseudonitrosite and furoxanes. [DOS 2336403; Imperial Chemical Industries, London (England)]

[PR 223 IE—D]

Dialkylaminomethane-triphosphonic acid esters *(2)* are made by the reaction of dichloromethylene-dialkylammonium chlorides *(1)* and trialkyl phosphites, preferably in the molar ratios of 1:3 to 1:4.5. Since the reaction is very vigorous, the com-



(1) *(2)*

R^1, R^2, R^3 = Alkyl (C_1 - C_4)

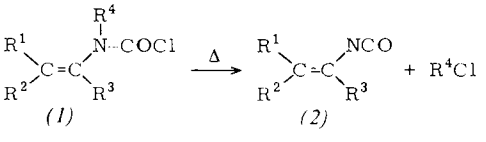
ponents are suitably reacted together in the form of solutions or suspensions in inert solvents at −80 to −20 °C. The phosphonic esters *(2)* have a flameproofing action on cellulose fibers. In addition, they can be used as stabilizers for polymers and for extracting heavy metal salts from aqueous solutions. [DOS 2237879; Henkel & Cie GmbH, Düsseldorf]

[PR 224 IE—D]

Inorganic-organic plastics of high strength, elasticity, shape stability on heating, and difficult flammability can be obtained by mixing aqueous, preferably 32—54%, silicate solutions with organic prepolymers which contain at least one other ionic group. The preferred organic prepolymer-ionomers are ionically modified isocyanates which simultaneously act as hardeners for the silicate component on account of the carbon dioxide produced by the NCO-water reaction. Macroscopically homogeneous plastics are formed, which consist of an ionomer-polysilica gel-binder material present as a colloidal xerosol. The process lends itself to the preparation of overlays, laminates, and packings, and in particular, when a propellant is added, to the manufacture of aerosol foams. [DOS 2227147; Bayer AG, Leverkusen]

[PR 225 IE—D]

1-Alkenyl isocyanates *(2)*, for example vinyl isocyanate [*(2)*, $R^1 = R^2 = R^3 = H$], can be obtained in good yield by the thermal cleavage of carbamyl chloride *(1)*, preferably at 30 to



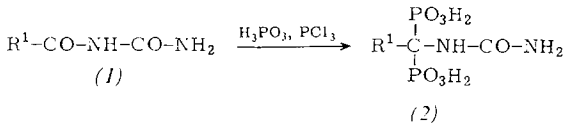
(1) *(2)*

R^1, R^2, R^3 = H, alkyl, aryl; R^4 = cycloalkyl, aryl, or CHR^5R^6; R^5, R^6 = alkyl, aryl, or R^5: R^5 = aryl, R^6 = H

150 °C and in the presence of metal compounds such as zinc chloride or zinc cyanide. The compounds *(1)* can be made from Schiff bases and phosgene. [DOS 2247724; BASF AG, Ludwigshafen]

[PR 226 IE—D]

1-Ureidoalkane-1,1-diphosphonic acids *(2)* are good complexing agents for multivalent metal ions and can be used in washing and cleansing agents as builders in place of polyphosphates.



R^1 = H or lower alkyl

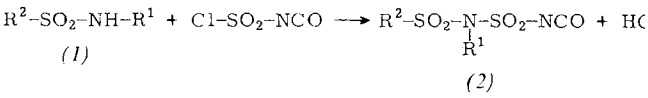
The phosphonic acids *(2)* can be obtained from acylureas *(1)* by warming with a mixture of phosphorous acid and phosphorus trichloride. [DOS 2254095; Joh. A. Benckiser GmbH, Ludwigshafen]

[PR 227 IE—D]

δ-Ketocarboxylic acid esters are obtained in good yield from α,β-unsaturated carboxylic esters, such as an alkyl acrylate, and ketones containing at least one hydrogen in the α position *e.g.* acetone or cyclohexanone. The addition is catalyzed by a primary amine or a Schiff base and a small amount of an acidic compound, *e.g.* benzoic acid, is added to the reaction mixture. [DOS 2355859; Stamicarbon B.V., Geleen (Netherlands)]

[PR 229 IE—D]

Sulfonylaminosulfonyl isocyanates *(2)* can be made by the reaction of sulfonamides *(1)* with chlorosulfonyl isocyanate, prefer-



R^1 = (cyclo)alkyl
R^2 = (subst.) alkyl or aryl

ably in the temperature range 100—160 °C. [DOS 2257240; Farbwerke Hoechst AG, Frankfurt/M.]

[PR 228 IE—D]

BOOK REVIEWS

MTP International Review of Science. Physical Chemistry: Series One. Edited by *A. Maccoll*. Vol. 5: Mass Spectrometry. Butterworths, London, and University Park Press, Baltimore, 1972. 1st edit., iii, 300 pp., 19 figures, bound, £ 10.00.

The title "Mass Spectrometry", even in combination with the series name "Physical Chemistry", appears to be too broad and misleading. The book consists of a collection—unquestionably well selected—of eight separate and unconnected review-type chapters on different types of ionization and ion-molecule reactions within mass spectrometry, which are not even linked by a common keyword index. Nor do the individual chapters attempt to be comprehensive as a rule: "This review aims to be selective rather than exhaustive" (*Robertson*, p. 107). "This review attempts to cover only a fraction of the subject implied by its title" (*Wahrhaftig*, p. 1). The common element consists in the authors' devoting their primary interest to the examination of reaction kinetics; unlike many others, they do not dwell on descriptions of the instrumentation or methods of measurement, as is evident from the small number of illustrations. A more precise title, such as "Selected Chapters on Ionization and Reaction Kinetics in Mass Spectrometry" would therefore have been preferable.

The numerous references, which go up to 1971, will be particularly valuable for the reader who purchases the volume as a result of coincidental interest in several of the chapters. In some cases they are of vital importance; thus, the "Theory of Mass Spectra" (Chapter 1, *A. L. Wahrhaftig*, 114 references) on 24 pages can be no more than sketchy, and for more detailed work the reader must be directed to "existing review articles". The author excuses his favored treatment of quasi-equilibrium theory: "The reviewer admits his bias, but does hope it has not unduly affected his judgment".

The three chapters on the formation of ions, on the other hand, are considerably more meaningful and detailed: "Ionization and Appearance Potentials" (Chapter 2, *J. D. Morrison*, 30 pp., 212 references), which deals with ionization by electron impact, "Field Ionization" (Chapter 4, *A. J. B. Robertson*, 31 pp., 142 references), and "Chemical Ionization Mass Spectrometry" (Chapter 5, *F. H. Field*, 49 pp., 56 references). Chapter 3, "Recent Advances in Electron Spectroscopy", appears out of place in the series but gives a clear description, accompanied by many references, of photoelectron spectroscopy and spectroscopy with electrons which originate from electron impact, Auger, autoionization, and Penning processes (*C. E. Brion*, 48 pp., 448 references). This is followed by chapters on two separate techniques for the investigation of ion-molecule reactions, "Ion Cyclotron Resonance Mass Spectrometry" (Chapter 6, *C. J. Drewery, G. C. Goode, K. R. Jennings*, 35 pp., 98 references) and "Time-of-flight Mass-Spectrometry" (Chapter 7, *R. S. Lehrle* and *J. E. Parker*, 40 pp., 337 references), and finally on "Metastable Ions in Mass Spectrometry" (Chapter 8, *J. L. Holmes* and *F. M. Benoit*, 42 pp., 173 references).

In general, most of the chapters appear to give a useful survey of the topic under discussion, but the book will only truly benefit the reader prepared to go single-mindedly through the original literature.

Jochen Franzen [NB 219 IE]

Chromatography of Environmental Hazards. Vol. 1. Carcinogens, Mutagens, and Teratogens. By *L. Fishbein*. Elsevier Publishing Company, Amsterdam—London—New York 1972, 1st edit., vii, 490 pp., 210 tables, bound $ 42.25.

This volume, the first of a planned three-volume series on the analytical detection of toxic substances in the human environment, concentrates on those chemicals which cause cancer, mutations, and malformations. They include alkylating agents (nitrosamines, aziridines, epoxides, aldehydes, lactones, phosphoric esters, and pyrrolizidine alkaloids), pesticides (not DDT!), pharmaceuticals, food impurities and additives, and several other toxins such as hydrazines, naphthylamines, urethanes, and peroxides. The analytical methods of detection are limited to paper, thin-layer, and gas chromatography for separation, and corresponding methods of identification. The material is presented very clearly and with the requisite degree of detail, with the result that in most cases supplementary reading of the original literature (partially included up to 1971) does not appear necessary. (Unfortunately, references are given only in the text, and not in the many tables.)

The classification of individual substances as carcinogens, mutagens, and/or teratogens appears somewhat questionable. No indication is given of the criteria for this classification in the form of tables, though there are copious literature references. However, a clear definition of such criteria is just what the chemist needs; for example, reference should have been made to the ambiguity of mutagenicity tests in microorganisms. Formaldehyde is thus classified as a carcinogen, which will hardly be subscribed to by an expert in chemical carcinogenesis. The cytostatic Endoxan, on the other hand, though undoubtedly carcinogenic, appears only as a mutagen and teratogen. Nor does it seem consistent to exclude from this volume the important class of carcinogenic polycyclic hydrocarbons of the 3,4-benzpyrene type; these were left for Volume 2.

Despite these minor defects the publication of this book should be welcomed, since it makes the chemist familiar with toxic pollutants and gives the biologist and the doctor an introduction to and directions for the determination of these substances. It is therefore hoped that the work will find widespread distribution.

Rudolf Preussmann [NB 223]

Bindung, Struktur und Reaktionsmechanismen in der organischen Chemie (Bonding, Structure and Reaction Mechanisms in Organic Chemistry). By *Ivan Ernest*. Springer-Verlag, Vienna—New York 1972. 1st edit., x, 389 pp., 6 figures, bound DM 98.—.

This work represents an attempt at summarizing the ever-growing field of physical organic chemistry. As a result of its limited size some of the aspects are discussed in insufficient detail, but each chapter gives numerous references to original papers, review articles, and monographs.

The book contains a brief introduction to the fundamental concepts of molecular orbital theory, of the types of bonds and stereochemistry, as well as a discussion of the characteristics and classification of organic reactions. Current methods of investigation are cited. The core of the book consists of the treatment of polar, radical, and orbital symmetry-controlled reactions; particularly the first two are discussed critically and in great detail. Recent views on reaction mechanisms, *e.g.* on S_N2 reactions, are also included. The chapter on multicenter reactions was deliberately kept brief by the author, since several monographs have recently appeared on this subject.

The reviewer considers this to be a clear and didactically well-written work. Only a few errors or obscurities have crept in, as *e.g.* in the discussion on the resonance forms of *cis* and *trans*-butadiene (p. 22). Its study is specially recommended to undergraduates. In view of its high price, an inexpensive paperback edition would be welcome.

M. T. Reetz [NB 226 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal.

Methoden der Analytischen Chemie. Eine Einführung. Vol. 1: Trennungsmethoden. By *R. Bock*. Verlag Chemie, Weinheim 1974. 362 pp., bound, DM 42.—.

Separation and Purification Methods, Vol. 2. Edited by *E. S. Perry, C. J. van Oss*, and *E. Grushka*. Marcel Dekker, New York 1974. xi, 466 pp., bound, $ 22.50.

Advances in Structure Research by Diffraction Methods—Fortschritte der Strukturforschung mit Beugungsmethoden, Vol. 5. Edited by *W. Hoppe* and *R. Mason*. Pergamon Press, New York/Friedr. Vieweg and Sohn, Braunschweig 1974. 120 pp., bound, DM 36.—.

Emulsions and Emulsion Technology, Part I. Edited by *K. J. Lissant*. Vol. 6 of the series "Surfactant Science Series". Edited by *M. J. Schick* and *F. M. Fowkes*. Marcel Dekker, New York 1974. xii, 440 pp., bound, $ 39.50.

Fluorocarbon and Related Chemistry, Vol. 2. Senior Reporters: *R. E. Bank* and *M. G. Barlow*. The Chemical Society, London 1974. viii, 491 pp., bound, £16.00.—A volume of the series "Specialist Periodical Reports".

Problems in Chemistry—Revised and Expanded. By *H. O. Daley, Jr.* and *R. F. O'Malley*. From the series "Undergraduate Chemistry". Edited by *J. J. Lagowski*. Marcel Dekker, New York 1974. xvii, 490 pp., stitched $ 7.95.

Synthetic Methods of Organic Chemistry, Vol. 28: Yearbook 1974. Edited by *W. Theilheimer*. S. Karger, Basel 1974. xx, 652 pp., bound, DM 466.—.

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Functional Monomers, Vol. 2. Edited by *R. H. Yocum* and *E. B. Nyquist*. Marcel Dekker, New York 1974. x, 817 pp., bound, £ 25.50.

Raman/IR Atlas organischer Verbindungen, Vol. 1. Published under the auspices of the Institut für Spektrochemie und Angewandte Spektroskopie, Dortmund. Edited by *B. Schrader* and *W. Meier*. Verlag Chemie, Weinheim 1974. xvii, xxxi pp., 300 Spectra, loose-leaf. Subscription price: DM 690.—, final price: DM 795.—.

Gmelins Handbuch der anorganischen Chemie. Supplemented 8. Edition. Vol. 14: Eisen-organische Verbindungen, Part A: Ferrocen 1. Springer-Verlag, Berlin 1974. vi, 395 pp., bound, DM 516.—.

^{13}C-NMR Spectroscopy. Methods and Applications. By *E. Breitmaier* and *W. Voelter*, Vol. 5 of the series "Monographs in Modern Chemistry". Edited by *H. F. Ebel*. Verlag Chemie, Weinheim 1974. xiii, 303 pp., bound, DM 98.—.

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NMR Basic Principles and Progress. Grundlagen und Fortschritte. Edited by *P. Diehl, E. Fluck*, and *R. Kosfeld*. Vol. 8: "Chemically Induced Dynamic Nuclear and Electron Polarizations—CIDNP and CIDEP". By *C. Richard* and *P. Granger*. Springer-Verlag, Berlin 1974. II, 127 pp., bound, DM 58.—.

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Handbuch der Spurenanalyse. Die Anreicherung und Bestimmung von Spurenelementen unter Anwendung chemischer, physikalischer und mikrobiologischer Verfahren. In two parts. By *O. G. Koch* and *G. A. Koch-Dedic*. Springer-Verlag, Berlin 1974. 2., completely revised and supplemented edit. xxiv, xiii, 1597 pp., bound, DM 498.—.

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Rückstandsanalytik von Pflanzenschutzmitteln. Mitteilung VI der Kommission für Pflanzenschutz-, Pflanzenbehandlungs- und Vorratsschutzmittel der Deutschen Forschungsgemeinschaft. 3. instalment 1974. Verlag Chemie, Weinheim. xliii, 164 pp., Loose-leaf collection, DM 68.—.

Electronic Structure and Magnetism of Inorganic Compounds, Vol. 3. Senior Reporter: *P. Day*. The Chemical Society, London 1974. xi, 433 pp., bound, £ 14.00.—A volume of the series "Specialist Periodical Reports".

An Introduction to Biochemical Reaction Mechanisms. By *J. N. Lowe* and *L. L. Ingraham*. From the series "Foundations of Modern Biochemistry Series". Prentice-Hall, Inc., Englewood Cliffs 1974. xiv, 145 pp., bound, £ 5.20.

Advances in Chromatography, Vol. 10. Edited by *J. Calvin Giddings* and *R. A. Keller*. Marcel Dekker, Inc., New York 1974. xi, 246 pp., bound, $ 19.75.

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The Theory of Pericyclic Reactions

By Nicoloas D. Epiotis[*]

Pericyclic reactions include thermal and photochemical cycloadditions and cycloreversions, electrocyclic reactions and sigmatropic shifts. Configuration interaction analysis can be used for making predictions about preferred reaction pathways, about reaction rates, about the nature of possible intermediate steps, and above all about the stereochemistry of such reactions.

1. Introduction

In 1965, in a series of preliminary communications, *Woodward* and *Hoffmann*[1] first enunciated the principle of the conservation of orbital symmetry in concerted reactions. Since the initial Woodward-Hoffmann contribution, there have been three major developments in the theory of pericyclic reactions:

The first development has been the publication of alternative theoretical schemes for the discussion of pericyclic reactions[2–9], all leading, with minor exceptions, to the same conclusions as the original Woodward-Hoffmann formulation. Of course, all these additional theoretical approaches differ in rigor, general applicability and conceptual simplicity but have served to sharpen our intuition in dealing with the intricate electronic factors which determine the outcome of a pericyclic reaction.

The second development has been the realization that the Woodward-Hoffmann rules can be modified depending on the electronic nature of the reactants, if one recognizes the importance of electronic configurations other than the lowest energy one in describing transition state complexes. In recent publications, we have discussed the importance of charge transfer configurations in thermal and photochemical cycloadditions[10] as well as the importance of doubly excited configurations in thermal pericyclic reactions of various types[11]. The discovery of the importance of configuration interaction in determining the electronic properties of transition states seems, in retrospect, to have been an inevitable discovery. Indeed, many years ago spectroscopists realized that the electronic transitions of molecules could be completely understood only on the basis of a theory which included configuration interaction as a key element[12]. In recent years, *Bader*[13], *Salem*[14], and *Pearson*[15] discussed the importance of excited states in determining the electronic properties of molecules and transition states. Thus, the development of new stereoselection rules based on configuration interaction theory was an inescapable step in the development of the original ideas of *Woodward* and *Hoffmann*. In addition to our work, one should mention the interesting contributions of *Baldwin*[16], *Michl*[17], and *Schmidt*[18] and the theoretical work of *Buenker* and *Peyerimhoff*[19], *Dewar*[20], *Trindle*[21], *Jackson*[22a], and *Raff* and *Porter*[22b] towards understanding how configuration interaction can modify our one configuration view of molecules and reactions.

The third development has been the realization that certain types of orbital interactions, other than frontier orbital interactions, can have some influence on the outcome of certain concerted reactions[23]. The last two developments are bound to stimulate further theoretical and experimental work in the area of pericyclic reactions and may lead to systematization of an enormous number of chemical facts.

In this progress report, a formal configuration interaction theory which can be used in either a semiquantitative or a qualitative sense for making predictions about preferred reaction pathways is presented. The emphasis has been placed on qualitative applications of the theory to stereochemical and rate aspects of pericyclic reactions and the aim has been the development of a general predictive scheme which can be readily put into test in the laboratory.

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2. Theory

In this work, we shall focus our attention on three general types of reactions:

a) Intermolecular cycloadditions.
b) Electrocyclic reactions.
c) Sigmatropic shifts.

A typical example of an intermolecular cycloaddition is the union of two ethylenes to form cyclobutane. The transition state of such a reaction involves the interaction of two molecules, namely, two ethylene molecules. A typical example of an electrocyclic reaction is the butadiene → cyclobutene transformation and the transition state of such a reaction involves the interaction of two formal molecular fragments, namely, the two ethylenic bonds of butadiene. Finally, a typical example of a sigmatropic shift is the 1,3 migration of carbon in 1-butene; the transition state of such a rearrangement involves the interaction of two formal radical fragments, namely, the migration framework (allyl radical) and the migrating group (methyl radical). In a general sense, most reactions involve the interaction of two fragments at the transition state and these fragments can be real or formal molecules. Unless the two fragments are identical, we can define one as the donor fragment D and the other as the acceptor fragment A[10]. The electronic states of the transition state complex DA involved in an intermolecular cycloaddition, an electrocyclic reaction, or, a sigmatropic shift can be described in terms of linear combinations of wavefunctions appropriate to the fragments D and A. In order to maximize the simplicity of the theory and yet retain the important features of our analysis, we may choose a minimal basis set of zero order configuration wavefunctions. The zero order configuration wavefunctions forming our basis set are:

1. The no bond configuration DA.
2. The locally excited configurations D*A and DA*.
3. The charge transfer configurations $D^{\oplus}A^{\ominus}$ and $D^{\ominus}A^{\oplus}$.

For brevity, we shall use the term configuration as an alternative term for zero order configuration wavefunction.

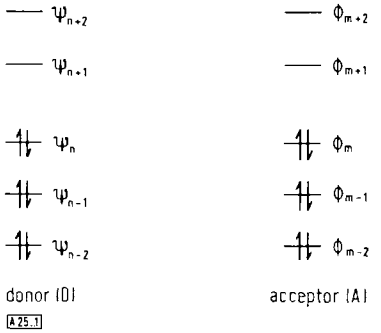


Fig. 1. Molecular orbitals of the donor (D) and acceptor (A) fragments.

The occupied and unoccupied MOs of the D and A fragments are shown in Fig. 1. By employing familiar quantum mechanical notation, we can write each configuration of the basis set in terms of the spin MOs of the two fragments.

In the above equations, A is the antisymmetrization operator. The presence of a dash above ψ or ϕ denotes a spin MO of α spin and the absence of a dash above ψ or ϕ denotes a spin MO of β spin. All five configurations are singlet configurations conforming to the Pauli Exclusion Principle. The energies associated with the five configurations can be written as follows:

$$E(DA) = 0 \quad (1)$$
$$E(D^{\oplus}A^{\ominus}) = -\varepsilon_n + \varepsilon_{m+1} - C = I_D - A_A - C \quad (2)$$
$$E(D^{\ominus}A^{\oplus}) = -\varepsilon_n + \varepsilon_{n+1} - C' = I_A - A_D - C' \quad (3)$$
$$E(D^*A) = -\varepsilon_n + \varepsilon_{n-1} \approx h\nu(n \rightarrow n+1) \quad (4)$$
$$E(DA^*) = -\varepsilon_m + \varepsilon_{m-1} \approx h\nu(m \rightarrow m+1) \quad (5)$$

In the above equations, ε is the SCF-MO energy, I_D is the lowest ionization potential of the donor, I_A is the lowest ionization potential of the acceptor, A_D is the electron affinity of the donor, A_A is the electron affinity of the acceptor, and C and C' are the electrostatic attractive interactions of the excess electron of one fragment with the electron hole of the other fragment and the rest of the symbols have their usual meaning.

We note at this point that, when the two fragments become identical, the charge transfer configurations and the locally excited configurations will have to be replaced by charge-resonance and excitation-resonance configurations[24], respectively. In such a case, the energies of the charge-resonance configurations will still be given by equations (2) and (3), while the energies of the excitation-resonance configurations will be given by equations (4) and (5) corrected for exciton type interaction[25] of the two fragments.

Inspection of equations (1)—(5) reveals that the quantities I_D, I_A, A_D, A_A, $h\nu\,(n \rightarrow n+1)$ and $h\nu\,(m \rightarrow m+1)$ can be extracted from experimental data and only C and C' need to be calculated explicitly[26]. Thus, we are in a position to rank the various configurations according to their relative energies as determined by reference to experimental data. These config-

urations represent the electronic states of the transition state complex in the hypothetical case of zero configuration interaction. Obviously, the real electronic states of the transition state complex result from the interaction between the various configurations and the difference in energy between a configuration and the corresponding electronic state arising from configuration interaction can be thought of as the stabilization or destabilization energy due to configuration interaction.

We can now consider explicitly how configurations interact to produce electronic states. Our first task is to define the Hamiltonian operator, remembering that we are dealing with reactions which involve simultaneous formation of more than one bond in the transition state.

$$H = H_D + H_A + H' \qquad (6)$$

In order to simplify our analysis, we adopt a Hamiltonian which consists of only one electron terms and we set out to develop electronic states which arise from one electron configuration mixing. In equation (6), H_D operates only on fragment D, H_A operates only on fragment A and H′ operates along the two or more forming bonds. Now, we can assume that the MOs of fragment D are orthogonal with respect to H_D and the MOs of fragment A are orthogonal with respect to H_A. Hence, H′ will be solely responsible for configuration mixing. A quantitative determination of the electronic states of a transition state complex DA can then be easily accomplished. Specifically, we can construct the energy matrix, where the diagonal elements are the energies of the zero order configurations and the off diagonal elements are the interaction terms between the zero order configurations. The important thing is that many of these matrix elements can be empirically evaluated by reference to experimental data. We can solve the corresponding secular determinant and get the eigenvalues and eigenvectors of the electronic state wavefunctions. The availability of high speed computers and the existence of ionization potential and spectroscopic data which can serve as empirical input make such configuration interaction calculations possible for systems of chemical interest.

While the theoretician might be interested in the subtle features of a problem which can only be revealed by explicit computation, the organic chemist is more interested in a general qualitative theory which can be directly applicable to problems of interest without the need of computer assistance. Hence, we should reduce the quantitative scheme for the determination of electronic states to a qualitative scheme which can still retain the important features of the theory. The various steps which one has to follow in attempting a qualitative configuration interaction analysis of chemical reactivity are given below:

Step 1. Rank the basis set configurations according to their relative energy. This can be implemented by means of equations (1) to (5).

Step 2. Construct the interaction matrix for the basis set configurations.

Step 3. Generate the electronic states of a given transition state complex by noting that the energy change of any two nondegenerate basis set configurations arising from their interaction will be inversely proportional to the energy difference between the two basis set configurations and directly proportional to the square of their interaction matrix element. The analogy between MO splitting, which is familiar to the organic chemist[27], and configuration splitting as a result of interaction is shown in Fig. 2.

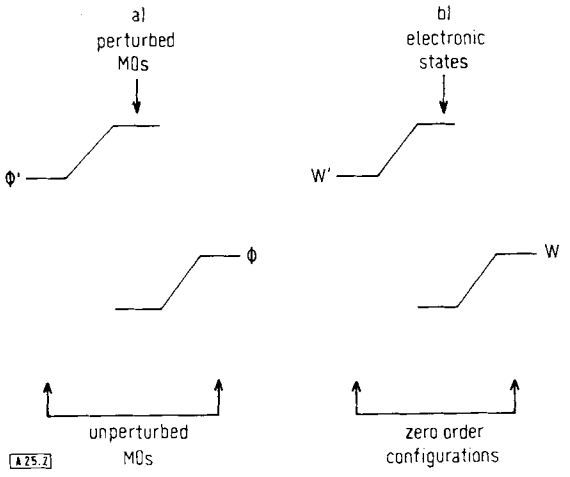


Fig. 2. a) MO interaction diagram, b) configuration interaction diagram. W and W′ are configurations.

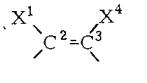
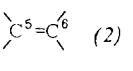
After these steps are completed, one can determine the preferred stereochemical course of a thermal reaction by comparing the relative energies of the lowest electronic states of the transition state complexes corresponding to different stereochemical modes of reaction. Similarly, one can determine the preferred stereochemistry of a photochemical reaction by comparing the relative energies of the first electronically excited states of the transition complexes corresponding to different stereochemical modes of reaction. Other reaction features can be determined in a similar manner[28].

We shall now consider how qualitative configuration interaction theory can be applied to $4n$ and $4n+2$ electron cycloadditions, electrocyclic reactions, and sigmatropic shifts. We shall try to determine the preferred stereochemistry of such reactions under the assumption that they are concerted and involve continuous bonding around the uniting atomic centers in the transition state. Such a transition state will be referred to as "pericyclic".

3. Intermolecular [2+2] Cycloadditions

3.1. Nonpolar Intermolecular [2+2] Cycloadditions

We first examine the case of nonpolar cycloadditions (AD) of *(1)* and *(2)*, where *(1)* is assumed to be the donor partner and *(2)* the acceptor partner. X is assumed to be a heteroatom with a lone pair of electrons in the p_z orbital.

(1)  *(2)* 

D A

In order to simplify the discussion, we assume that equal bond making between C^2 and C^5 and between C^3 and C^6 has taken place at the transition state. The one electron Hamiltonian is written as follows:

$$H = H_{(1)} + H_{(2)} + H'$$

where

$$H' = H_{25} + H_{36}$$

The basis set configurations for the [2+2] cycloaddition transition state complex are shown in Fig. 3. The corresponding wavefunctions can be written as Slater determinants in the manner illustrated in Section 2. The energy of the no bond configuration DA is the zero point on the energy scale. The next configuration in order of increasing energy is the charge transfer configuration $D^{\oplus}A^{\ominus}$. This configuration will necessarily have lower energy than the locally excited configurations D*A and DA* because the promotional energy $\varepsilon_3 - \varepsilon'_2$ in the $D^{\oplus}A^{\ominus}$ configuration is less than the promotional energies $\varepsilon_3 - \varepsilon_4$ and $\varepsilon'_1 - \varepsilon'_2$ in the D*A and DA* configurations respectively and also because the energy of the $D^{\oplus}A^{\ominus}$ configuration is further lowered on account of the coulombic attraction C of the two fragments. The relative energy of the locally excited configurations D*A and DA* will depend to a large extent on the energy difference between ϕ_3 and ϕ_4 in the donor partner and the energy difference between ψ_1 and ψ_2 in the acceptor partner. Finally, the charge transfer configuration $D^{\ominus}A^{\oplus}$ can have either higher or lower energy than one or both of the locally excited configurations D*A and DA* depending on the magnitude of the attractive coulombic term C' relative to the promotional energy term $\varepsilon'_1 - \varepsilon_4$.

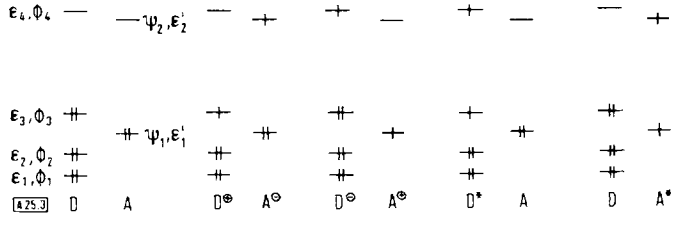


Fig. 3. Basis set configurations for a nonpolar [2+2] cycloaddition. D is the donor and A the acceptor fragment.

The next step is to construct the interaction matrix. This involves computing matrix elements between determinantal wave functions which can be easily accomplished by adhering to simple rules[29]. The interaction matrix is shown in Scheme 1[30].

	DA	D*A	DA*	$D^{\oplus}A^{\ominus}$	$D^{\ominus}A^{\oplus}$
DA	X				
D*A	0	X			
DA*	0	0	X		
$D^{\oplus}A^{\ominus}$	$\langle\phi_3\|H'\|\psi_2\rangle$	$\langle\phi_4\|H'\|\psi_2\rangle$	$\langle\phi_3\|H'\|\psi_1\rangle$	X	
$D^{\ominus}A^{\oplus}$	$\langle\phi_4\|H'\|\psi_1\rangle$	$\langle\phi_3\|H'\|\psi_1\rangle$	$\langle\phi_4\|H'\|\psi_2\rangle$	0	X

Scheme 1. Interaction matrix for a nonpolar [2+2] cycloaddition [30].

At this point, a brief digression would seem justifiable in order to consider the physical significance of matrix elements. In all cases of interest to us, the one electron operator H' responsible for configuration mixing operates along the two pairs of uniting atoms, say pair A and pair B. One can write H' as a sum of two one-electron operators, one (H_A) operating along pair A and another (H_B) operating along pair B.

$$H' = H_A + H_B$$

The matrix element of two configurations W_1 and W_2 with respect to H' can be written as

$$\langle W_1|H'|W_2\rangle = \langle W_1|H_A|W_2\rangle + \langle W_1|H_B|W_2\rangle$$

We distinguish the following cases of interest:

a) $\langle W_1|H_A|W_2\rangle$ and $\langle W_1|H_B|W_2\rangle$ are finite and have the same sign. In such a case $\langle W_1|H'|W_2\rangle$ in absolute magnitude is large, the two configurations mix strongly and there is pericyclic bonding, *e.g.* the resultant electronic state involves bonding interactions along both pairs of atoms.

b) $\langle W_1|H_A|W_2\rangle$ and $\langle W_1|H_B|W_2\rangle$ are finite but have opposite signs. In such a case $\langle W_1|H'|W_2\rangle$ is very small or zero, the two configurations mix slightly or not at all and there is no pericyclic bonding, *e.g.* the resultant electronic state involves a bonding and an antibonding interaction along the two pairs of atoms.

c) $\langle W_1|H_A|W_2\rangle$ is finite but $\langle W_1|H_B|W_2\rangle$ is zero. In such a case $\langle W_1|H'|W_2\rangle$ is still apreciable, the two configurations mix but there is no pericyclic bonding, *e.g.* the resultant electronic state involves a bonding and a nonbonding interaction along the two pairs of atoms. In all subsequent discussions, the matrix elements are evaluated with respect to H' and the resultant electronic states are designated pericyclic or nonpericyclic.

The π MOs of *(1)* and *(2)* are of the general form:

$$\phi_1 = C_{11}p_1 + C_{12}p_2 + C_{13}p_3 + C_{14}p_4$$
$$\phi_2 = C_{21}p_1 + C_{22}p_2 - C_{23}p_3 - C_{24}p_4$$
$$\phi_3 = C_{31}p_1 - C_{32}p_2 - C_{33}p_3 + C_{34}p_4$$
$$\phi_4 = C_{41}p_1 - C_{42}p_2 + C_{43}p_3 - C_{44}p_4$$

where

$$C_{11} = C_{14};\ C_{12} = C_{13}$$
$$C_{21} = C_{24};\ C_{22} = C_{23}$$
$$C_{31} = C_{34};\ C_{32} = C_{33}$$
$$C_{41} = C_{44};\ C_{42} = C_{43}$$

and

$$\psi_1 = C_{15}p_5 + C_{16}p_6$$
$$\psi_2 = C_{25}p_5 - C_{26}p_6$$

where

$$C_{15} = C_{16};\ C_{25} = C_{26}$$

In the above equations, $C_{\mu\nu}$ is the 2p AO coefficient of the νth atom of the μth MO and p_ν is the 2p AO of the νth atom. Because of the symmetry of *(1)* and *(2)*, one has the general relationships

$$C_{\mu 1} = C_{\mu 4}$$
$$C_{\mu 2} = C_{\mu 3}$$

and

$$C_{\mu 5} = C_{\mu 6}$$

The MO integrals of the half interaction matrix can be expanded into AO integrals. In this and all subsequent cases, the sign of the matrix element will not concern us since we shall be dealing with interactions of nondegenerate basis set configurations where the energy change is proportional to the square of the matrix element. Hence, we establish the convention of writing

all interaction matrix elements as positive quantities. In the case of a [2s+2s] cycloaddition (s=suprafacial), the MO integrals become:

$$\langle\phi_3|H'|\psi_2\rangle = 0$$
$$\langle\phi_4|H'|\psi_1\rangle = 0$$
$$\langle\phi_4|H'|\psi_2\rangle = 2C_{42}C_{25}\gamma_{25}$$
$$\langle\phi_3|H'|\psi_1\rangle = 2C_{32}C_{15}\gamma_{25}$$

where

$$\gamma_{25} = \langle p_2|H'|p_5\rangle;$$
$$\gamma_{36} = \langle p_3|H'|p_6\rangle$$

These resonance integrals are appropriate to [2s+2s] union so we can define:

$$\gamma_{25} = \gamma_{36} = \gamma_S$$

In the case of a [2s+2a] cycloaddition (a=antarafacial), the MO integrals become:

$$\langle\phi_3|H'|\psi_2\rangle = 2C_{32}C_{25}\gamma'_{25}$$
$$\langle\phi_4|H'|\psi_1\rangle = 2C_{42}C_{15}\gamma'_{25}$$
$$\langle\phi_4|H'|\psi_2\rangle = 0$$
$$\langle\phi_3|H'|\psi_1\rangle = 0$$

where

$$\gamma'_{25} = \langle p_2|H'|p_5\rangle;$$
$$\gamma'_{36} = \langle p_3|H'|p_6\rangle$$

These resonance integrals are appropriate to [2s+2a] union so we define:

$$\gamma'_{25} = \gamma'_{36} = \gamma_A$$

Accordingly, the half interaction matrices for [2s+2s] and [2s+2a] cycloadditions can be written as shown in Scheme 2.

a) [2s+2s]	DA	D*A	DA*	$D^{\oplus}A^{\ominus}$	$D^{\ominus}A^{\oplus}$
DA	X				
D*A	0	X			
DA*	0	0	X		
$D^{\oplus}A^{\ominus}$	0	$2C_{42}C_{25}\gamma_S$	$2C_{32}C_{15}\gamma_S$	X	
$D^{\ominus}A^{\oplus}$	0	$2C_{32}C_{15}\gamma_S$	$2C_{42}C_{25}\gamma_S$	0	X

b) [2s+2a]	DA	D*A	DA*	$D^{\oplus}A^{\ominus}$	$D^{\ominus}A^{\oplus}$
DA	X				
D*A	0	X			
DA*	0	0	X		
$D^{\oplus}A^{\ominus}$	$2C_{32}C_{25}\gamma_A$	0	0	X	
$D^{\ominus}A^{\oplus}$	$2C_{42}C_{15}\gamma_A$	0	0	0	X

Scheme 2. Half interaction matrices for [2s+2s] and [2s+2a] cycloadditions.

Examination of the two interaction matrices leads to the following conclusions:

1. In the case of [2s+2s] union, the locally excited configurations D*A and DA* can interact strongly with the charge transfer configurations $D^{\oplus}A^{\ominus}$ and $D^{\ominus}A^{\oplus}$ in order to produce the electronic states S_1, S_2, S_3 and S_4 which involve pericyclic bonding of the two cycloaddition partners. In contrast, the remaining electronic state S_0 is a single configuration state without pericyclic bonding. This last electronic state S_0 is a non-bonding state.

2. In the case of [2s+2a] union, the ground state configuration DA can interact weakly with the charge transfer configurations $D^{\oplus}A^{\ominus}$ and $D^{\ominus}A^{\oplus}$ in order to produce the electronic states A_0, A_1 and A_4 with pericyclic bonding of the two cycloaddition partners. In contrast, the remaining electronic states A_2 and A_3 are single configuration states without pericyclic bonding. A_2 and A_3 are non-bonding electronic states.

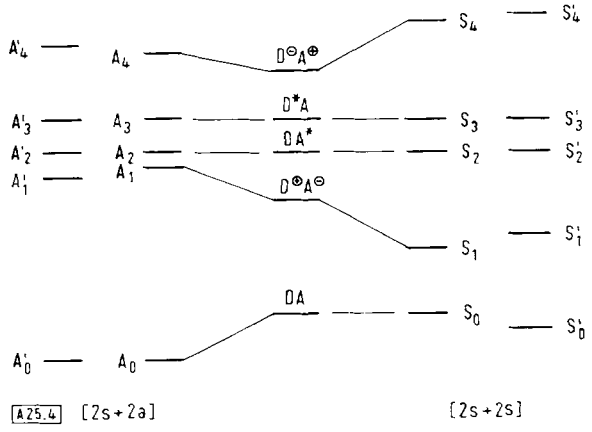


Fig. 4. Configuration interaction diagram for a nonpolar [2+2] cycloaddition. The S and A states refer to symmetrical cases and the S' and A' states to unsymmetrical cases.

These considerations can be simply understood by reference to Fig. 4 which illustrates how the basis set configurations interact to form the final electronic states of the [2s+2s] and [2s+2a] transition state complexes[31]. The configuration interaction diagram (Fig. 4) is constructed under the assumption that the resonance integrals for the [2s+2s] and the [2s+2a] union have the same magnitude.

$$\gamma_S = \gamma_A$$

This assumption simplifies the construction of the configuration interaction diagram and helps focusing our attention on the electronic factors responsible for configuration mixing. However, in addition to the configuration interaction diagram, we have to consider the steric features of [2s+2s] and [2s+2a] transition state complexes in order to assess reliably the relative energy of the corresponding electronic states.

The chemical implications of the configuration interaction diagram are straightforward:

1. A concerted nonpolar [2+2] cycloaddition will proceed thermally in a [2s+2a] manner because the lowest electronic state A_0 involves pericyclic bonding and has lower energy than the lowest electronic state S_0 which does not involve pericyclic bonding. The electronic stabilization of the [2s+2s] and [2s+2a] transition state complexes due to configuration interaction are:

$$SE(2s+2a) = E(A_0) - E(DA) > 0$$
$$SE(2s+2s) = E(S_0) - E(DA) = 0$$

Now, the magnitude of the electronic stabilization of the [2s+2a] transition state complex is small because the energy difference between the DA, $D^{\oplus}A^{\ominus}$ and $D^{\ominus}A^{\oplus}$ configurations is large. Furthermore, the [2s+2a] transition state complex is sterically destabilized. Accordingly, *one may expect that*

a diradical mechanism can dominate a concerted [2s+2a] union of the cycloaddends in thermal nonpolar [2+2] cycloadditions.

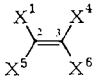
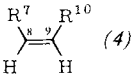
2. A concerted nonpolar [2+2] cycloaddition will proceed photochemically in a [2s+2s] manner because the first excited electronic state S_1 is of lower energy than the first electronic state A_1 and both states involve pericyclic bonding. Furthermore, steric destabilization of the excited electronic states of the [2s+2a] transition state complex, if any, can only serve to accentuate the preference for [2s+2s] over [2s+2a] union. The S_1 state has excimer character[32] since it is a mixture of charge transfer and locally excited configurations, while the A_1 state has charge transfer character[33] since it is a mixture of no bond and charge transfer configurations. Finally, we note that S_1 involves strong pericyclic bonding and A_1 involves weak pericyclic bonding. This arises because S_1 is the product of strong configuration mixing, while A_1 is not.

The theoretical analysis presented above is appropriate for nonpolar cycloadditions of two symmetrical molecules involving equal bond formation at the transition state. In practice, one or both cycloaddends can be unsymmetrically substituted and the cycloaddition may involve unequal bond making at the transition state. Under these circumstances, certain MO integrals can become nonzero, albeit small in magnitude. The result is that additional configuration mixing can take place and this is illustrated in Fig. 4. Calculations show that in most cases the asymmetry induced configuration mixing is small and can be neglected when one aims at qualitative generalizations[34]. Inspection of Fig. 4 reveals that the asymmetry induced configuration mixing does not alter our qualitative conclusions.

There is a subtle feature involved in asymmetry induced configuration mixing which can be best understood by reference to a specific case. For example, in the case of nonpolar [2s+2s] cycloaddition the no bond configuration DA cannot mix with any of the other configurations when the transition state complex has high symmetry. Now, the absence of symmetry allows DA to mix to a small extent with $D^{\oplus}A^{\ominus}$ and $D^{\ominus}A^{\oplus}$ and generate the electronic state S'_0. In most cases, such induced mixing does not result in pericyclic bonding. Instead, there is a bonding interaction between two centers and an antibonding interaction between the other two centers, the former being stronger than the latter. As a result, asymmetry induced configuration mixing serves to lower the energy of S'_0 relative to S_0 but does not result in pericyclic bonding. To put it crudely, asymmetry induced mixing transforms a nonbonding state into a slightly bonding state but not into a pericyclic state. This discussion is applicable to all other subsequent cases where asymmetry induced mixing is a realistic possibility.

3.2. Polar Intermolecular [2+2] Cycloadditions

We now proceed to examine the case of polar (AX) cycloaddition of *(3)* and *(4)*, where *(3)* is assumed to be the donor partner and *(4)* the acceptor partner. X is a heteroatom with a lone pair in the p_z orbital and R is an electron acceptor substituent.

(3)  *(4)* 

D A

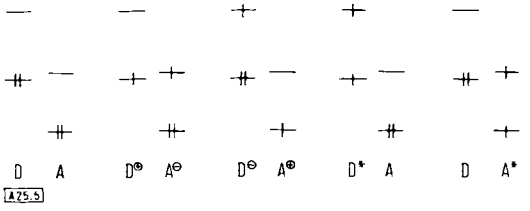
Again, in order to simplify the discussion, we assume that equal bond making between C^2 and C^8 and between C^3 and C^9 has taken place at the transition state. The one electron Hamiltonian is written as follows:

$$H = H_{(3)} + H_{(4)} + H'$$

where

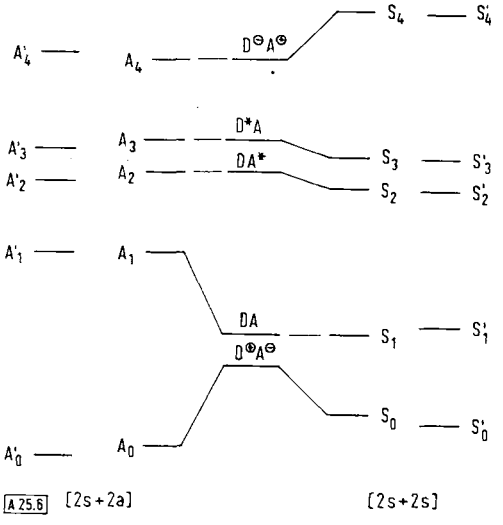
$$H' = H_{28} + H_{39}$$

Our analysis proceeds in exactly the same manner as in the case of nonpolar cycloadditions. The basis set configurations for the [2+2] cycloaddition transition state complex are shown in Fig. 5. The corresponding wave functions can be written as Slater determinant wave functions. The relative energies of the basis set configurations are shown in Fig. 6. The situation is similar to that encountered in nonpolar [2+2] cycloadditions, with one important difference: *in polar [2+2] cycloadditions, the charge transfer configuration $D^{\oplus}A^{\ominus}$ can be the configuration of lowest energy, e.g.* there is a reversal in the relative energy ordering of the $D^{\oplus}A^{\ominus}$ and DA configurations. In general, as one goes from a nonpolar to a polar [2+2] cycloaddition, the energy of the $D^{\oplus}A^{\ominus}$ configuration decreases. At the limit of a very polar cycloaddition, the energy of the $D^{\oplus}A^{\ominus}$ configuration can be lower than the energy of the DA configuration.



A 25.5

Fig. 5. Basis set configurations for a polar [2+2] cycloaddition. D is the donor and A the acceptor fragment. Only the HOMO and LUMO of the donor and acceptor fragments are shown.

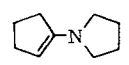


A 25.6

Fig. 6. Configuration interaction diagram for a polar [2+2] cycloaddition. The S and A states refer to symmetrical cases and the S' and A' states to unsymmetrical cases.

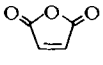
It is interesting to investigate the conditions for energy equality between the $D^{\oplus}A^{\ominus}$ and DA configurations. In typical [2+2]

cycloadditions, the magnitude of the coulombic term C ranges between three and six electron volts[35]. Hence, one can qualitatively expect that the energy of the $D^{\oplus}A^{\ominus}$ configuration can be lower than the energy of the DA configuration whenever the quantity $I_D - A_A$ has a value between three and six electron volts. This latter condition is met when the two cycloaddends are a good donor olefin and a good acceptor olefin. For example, the ionization potential I_D of a good donor[36] and the electron affinity A_A of a good acceptor olefin[37] are shown below. The quantity $I_D - A_A$ is calculated to be 4.44 eV. Even lower values are expected for better donors and acceptors.



(5)

I_D = 7.33 eV



(6)

A_A = 2.89 eV

The possibility that the charge transfer configuration $D^{\oplus}A^{\ominus}$ can have higher, equal, or lower energy than the no-bond DA configuration has been emphasized by *Kosower* in his discussion of charge transfer complexes[38].

We wish to emphasize that the estimates of the energy of the $D^{\oplus}A^{\ominus}$, $D^{\ominus}A^{\oplus}$, DA* and D*A configurations are conservative. At the transition state, the olefinic bonds are stretched in the process of forming the cyclobutane adduct. Bond stretch gives rise to increased HOMO energy and decreased LUMO energy, *e.g. at the transition state a molecule is a better donor and acceptor relative to the same molecule in its equilibrium state.* As a result, the $D^{\oplus}A^{\ominus}$, $D^{\ominus}A^{\oplus}$, D*A and DA* configurations will have even lower energy than the ones calculated on the basis of data pertaining to the two cycloaddends in their equilibrium state[39].

We can now proceed to examine how the basis set configurations interact in order to form the final electronic states. By following the same procedure as in the case of nonpolar [2+2] cycloaddition, we can construct the general interaction matrix, expand the molecular orbital integrals into atomic orbital integrals and arrive at the interaction matrices for [2s+2s] and [2s+2a] union of the two cycloaddends. The resultant electronic states are shown in Fig. 6. Once more, the configuration interaction diagrams (Fig. 6) are constructed under the assumption that $\gamma_S = \gamma_A$. It can be seen that the states A_0, A_1, A_4, S_0, S_2, S_3, and S_4 involve pericyclic bonding, while the states A_2, A_3, S_1 do not involve pericyclic bonding. An examination of the configuration interaction diagram leads to the following conclusions:

1. Unlike a concerted nonpolar [2+2] cycloaddition, a concerted polar [2+2] cycloaddition can proceed thermally in a [2s+2s] manner because both S_0 and A_0 electronic states involve pericyclic bonding. The electronic stabilization of the [2s+2s] and [2s+2a] transition state complexes due to configuration interaction are:

$$SE(2s+2a) = E(A_0) - E(D^{\oplus}A^{\ominus}) > 0$$
$$SE(2s+2s) = E(S_0) - E(D^{\oplus}A^{\ominus}) > 0$$

Now, the magnitude of the electronic stabilization of the [2s+2a] transition state complex is greater than the magnitude of the electronic stabilization of the [2s+2s] transition state complex due to configuration interaction. This is primarily due to a small energy separation of the DA and $D^{\oplus}A^{\ominus}$ configurations and a larger energy separation of the $D^{\oplus}A^{\ominus}$ and D*A and DA* configurations. On the other hand, the [2s+2a] transition state complex is sterically destabilized to a very large extent relative to the [2s+2s] transition state complex. Hence, a combination of the two effects is almost certain to lead to S_0 having a lower energy than A_0. The electronic stabilization of concerted [2s+2s] union and its favorable steric features lead one to expect that *polar [2+2] cycloadditions will occur thermally in a concerted [2s+2s] manner.*

2. A concerted polar [2+2] cycloaddition will proceed photochemically in a [2s+2a] manner because the first excited electronic state A_1 involves pericyclic bonding while the first excited electronic state S_1 does not; *e.g.* S_1 is a non-bonding state. Furthermore, A_1, the lowest excited state involving [2s+2a] pericyclic bonding, has lower electronic energy than S_2, the lowest excited state involving [2s+2s] pericyclic bonding. Whenever steric destabilization of the excited electronic states of the [2s+2a] transition state complex is small, A_1 will have lower energy than S_2. Once again, we note that S_2, the lowest excited state of the [2s+2s] transition state complex, has excimer character, while A_1, the lowest excited state of the [2s+2a] transition state complex, has charge transfer character. Finally, we note that A_1 involves strong pericyclic bonding and S_2 involves weak pericyclic bonding.

Asymmetry induced mixing can be present in polar [2+2] cycloaddition. In the case that one or both cycloaddends are unsymmetrically substituted or the cycloaddition involves unequal bond making at the transition state, certain integrals can become nonzero, albeit small in magnitude. The result is that additional configuration mixing can take place; this is illustrated in Fig. 6. Again, this effect is small in magnitude and can be neglected when one aims at qualitative generalizations. Inspection of Fig. 6 reveals that the asymmetry induced configuration mixing does not alter our qualitative conclusions.

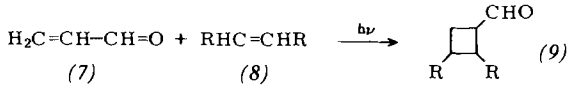
There are two important classes of photochemical [2+2] nonpolar cycloadditions which merit special attention:

1. Nonpolar [2+2] photocycloadditions involving $n\pi^*$ excitation of one cycloaddend.

2. Nonpolar [2+2] photocycloadditions involving a photoexcited carbonyl group.

We shall examine these two cases in some detail.

A nonpolar [2+2] photocycloaddition involving $n\pi^*$ excitation of one cycloaddend is typified by the reaction of *(7)* and *(8)* to give *(9)*.



(7) *(8)* *(9)*

R = CN, CHO, COOR', etc.

In such a reaction, the $n\pi^*$ excited enone *(7)* attacks an electron poor olefin *(8)* in its ground state. In this reaction, the singly occupied nonbonding orbital of the photoexcited enone does not participate in the reaction; *e.g.* it is only the olefinic bond of the photoexcited enone which is involved

in the photocycloaddition. Hence, the excited electronic states of the transition state complex can only be constructed from zero order configurations which have a singly occupied nonbonding orbital in the enone. The important configurations of this type are shown in Fig. 7 and the corresponding configuration interaction diagram is shown in Fig. 8. It is clear that such photoreactions must be [2s+2s] stereoselective.

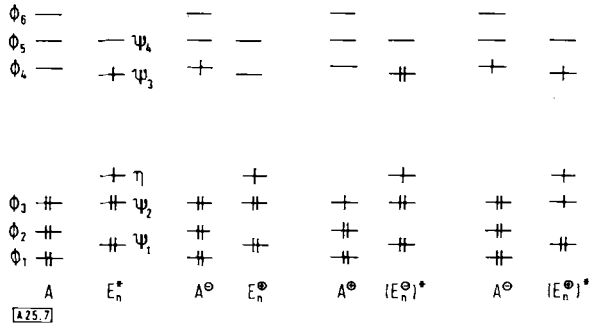


Fig. 7. Basis set configurations for a nonpolar [2+2] photocycloaddition of an nπ* excited enone to an electron acceptor olefin. E denotes the enone fragment and A the acceptor olefin fragment.

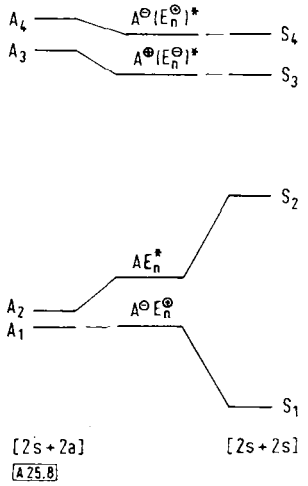
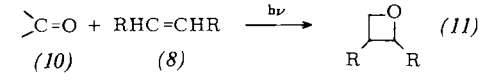


Fig. 8. Configuration interaction diagram for a nonpolar [2+2] photocycloaddition of an nπ* excited enone to an acceptor olefin.

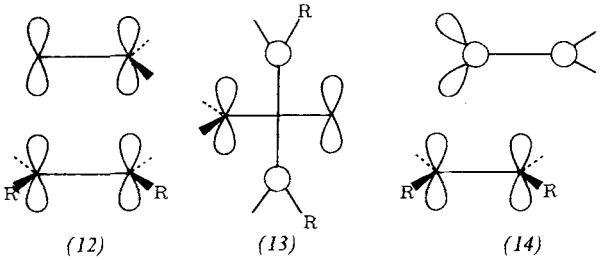
A nonpolar [2+2] photocycloaddition of a photoexcited carbonyl is typified by the reaction *(10)* + *(8)* → *(11)*.



(10) *(8)* *(11)*

R = CN, CHO, COOR', etc.

In this reaction, either the n or π electrons of the carbonyl group can be involved in the photocycloaddition. As a result, there are three possible transition state geometries: *(12)*, *(13)*, and *(14)*.



(12) *(13)* *(14)*

The basis set configurations (Fig. 9) include both nπ* and ππ* excited configurations.

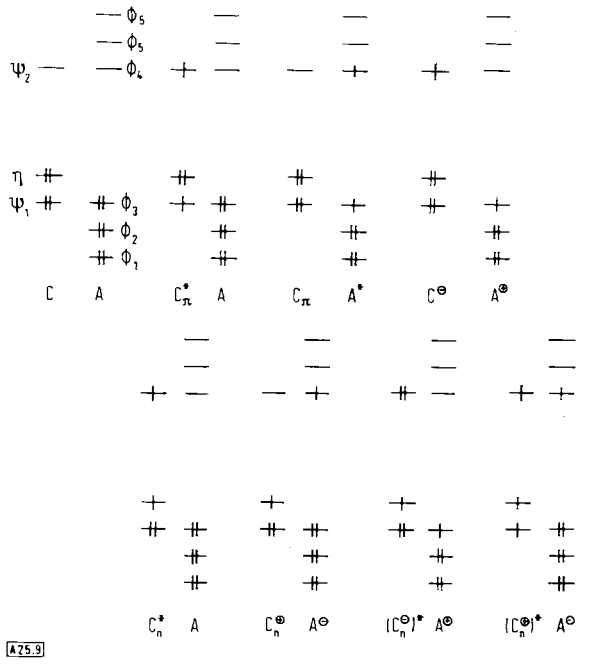


Fig. 9. Basis set configurations for a nonpolar [2+2] photocycloaddition involving a carbonyl group. C denotes the carbonyl fragment and A the acceptor olefin fragment.

Now, if the photocycloaddition is initiated by nπ* excitation of the carbonyl group, then the appropriate excited states of the photocycloaddition transition state complex are constructed from the zero order configurations which mix with the C_n^*A configuration (C signifies carbonyl group). The corresponding general interaction matrix is shown in Scheme 3.

	CA	C_n^*A	$C_n^{\oplus}A^{\ominus}$	$(C_n^{\ominus})^*A^{\oplus}$	$(C_n^{\oplus})^*A^{\ominus}$	$C^{\ominus}A^{\oplus}$
CA	X					
C_n^*A	0	X				
$C_n^{\oplus}A^{\ominus}$	$\langle n\|H\|\phi_4\rangle$	$\langle\psi_2\|H\|\phi_4\rangle$	X			
$(C_n^{\ominus})^*A^{\oplus}$	0	$\langle\psi_2\|H\|\phi_3\rangle$	0	X		
$(C_n^{\oplus})^*A^{\ominus}$	0	$\langle\psi_1\|H\|\phi_4\rangle$	0	0	X	
$C^{\ominus}A^{\oplus}$	$\langle\phi_3\|H\|\psi_2\rangle$	$\langle n\|H\|\phi_3\rangle$	0	0	0	X

Scheme 3. General interaction matrix for a nonpolar [2+2] photocycloaddition involving a carbonyl group.

The resulting configuration interaction diagram is shown in Fig. 10. In this case, as in Fig. 12 and Fig. 13, the $C^{\ominus}A^{\oplus}$ ($C^{\ominus}D^{\oplus}$) configuration does not take part in the formation of the [2s+2s] and [2s+2a] states, since it cannot mix with the other configurations and would represent a high nonbonding state. It follows that nonpolar [2+2] photocycloadditions involving the carbonyl group will be [2s+2s] stereoselective[40]. On the other hand, if the photocycloaddition is initiated by ππ* excitation of the carbonyl group or the olefin, then the appropriate excited states of the photocycloaddition transition state complex are constructed from the zero order configurations which mix with the C_n^*A or $C_\pi A^*$ configurations. The latter two cases are identical to the case of nonpolar [2+2] photocycloaddition of two simple olefins which was discussed before. An important aspect of these photocycloadditions is that asymmetry at the transition state can intermix nπ* and ππ* excited configurations. If such an

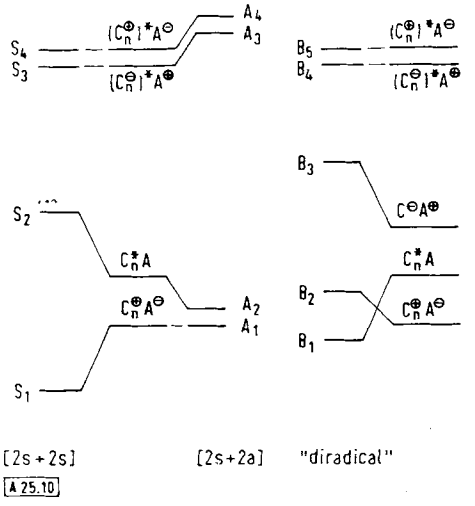


Fig. 10. Configuration interaction diagram for a nonpolar [2+2] photocycloaddition of an nπ* excited carbonyl to an acceptor olefin. The states B_0—B_5 refer to a pseudodiradical.

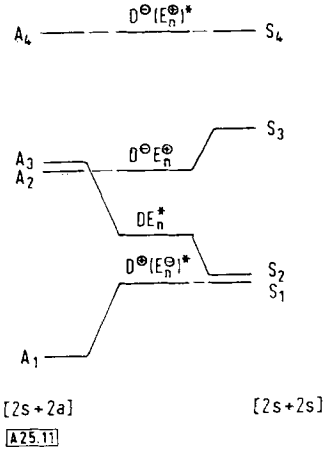
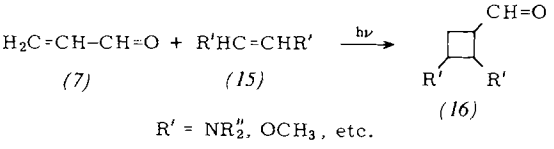


Fig. 11. Configuration interaction diagram for polar [2+2] photocycloaddition of a donor olefin (D) to an nπ* excited enone (E).

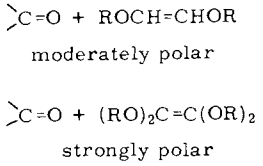
asymmetry induced configuration mixing is present to a large extent, either nπ* or ππ* photoexcitation can lead to similar products by proceeding through the same excited transition state complex. However, it should be pointed out that such asymmetry induced mixing still leads to the prediction that nonpolar cycloadditions of excited carbonyl will be [2s+2s] stereoselective.

Finally, we examine the interesting cases of polar [2+2] photocycloadditions involving nπ* excitation of one cycloaddend and polar [2+2] cycloadditions involving an excited carbonyl group. A typical reaction of the former type is the reaction of *(7)* with *(15)* to give *(16)*.



Here, the nπ* excited enone *(7)* attacks the electron rich olefin *(15)* in its ground state. Again, the excited electronic states of the transition state complex can only be constructed from zero order configurations which have a singly occupied nonbonding orbital in the enone. The configuration interaction diagram (Fig. 11) indicates that, unless steric prohibitions are great, such reactions will be [2s+2a] stereoselective.

An interesting situation arises in the case of polar [2+2] photocycloaddition of an excited carbonyl group. Specifically, one can distinguish modestly polar and extremely polar photoreactions which, as we shall see, are associated with different stereoselectivities.



The basis set configurations are constructed in the usual manner and include both nπ* and ππ* excited configurations. Subsequently, the general interaction matrix is developed and, if the photocycloaddition is initiated by nπ* excitation of the carbonyl group, the appropriate excited states of the photocycloaddition transition state complex are constructed from zero order configurations which mix with the C_n^*D configuration. The resulting configuration interaction diagrams (Fig. 12 and 13) indicate that modestly polar [2+2] photocycloadditions involving nπ* excitation of the carbonyl group will occur *via* a pseudodiradical[40], while extremely polar reactions of the same type will be [2s+2a] stereoselective. On the

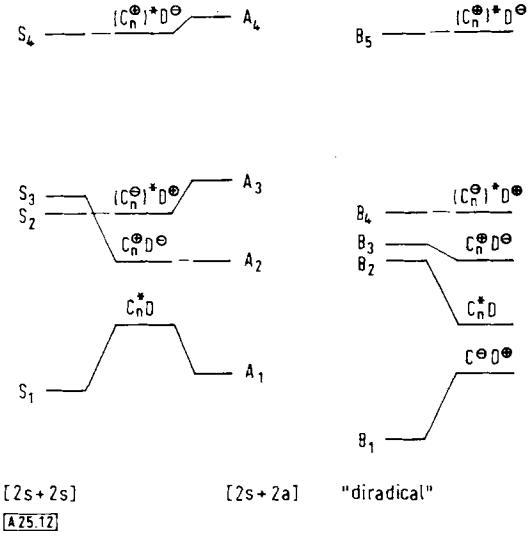


Fig. 12. Configuration interaction diagram for a modestly polar [2+2] photocycloaddition of a donor olefin (D) to an nπ* excited carbonyl group (C). The states B_0—B_5 refer to a pseudodiradical.

other hand, if the photocycloadditions are initiated by ππ* excitation of the carbonyl group or the olefin, then the appropriate excited states of the photocycloaddition transition state complex are constructed from zero order configurations which mix with the C_π^*D or $C_\pi D^*$ configurations. These latter two cases are identical to the case of polar [2+2] photocycloaddi-

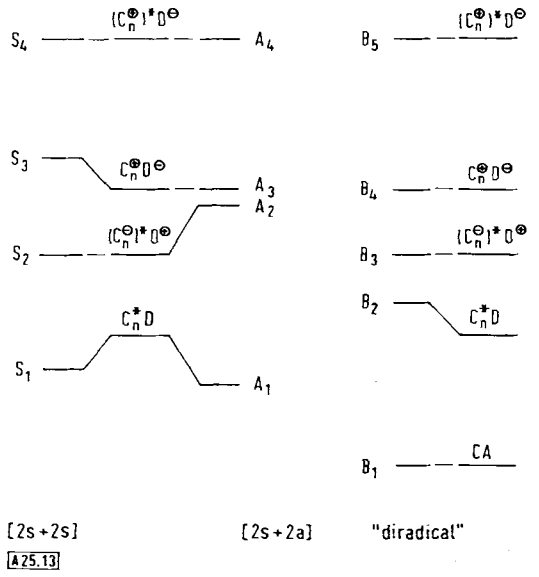
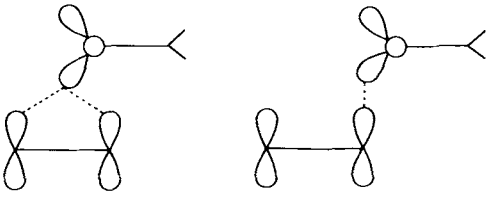


Fig. 13. Configuration interaction diagram for a highly polar [2+2] photocycloaddition of a donor olefin (D) to an $n\pi^*$ excited carbonyl group (C).

tion of two simple olefins which was discussed before. Once again, the reader is reminded that asymmetry induced mixing can be important in the photoreactions of the carbonyl group. Such mixing will give rise to a diradical mechanism in modestly polar photocycloadditions and to a [2s+2a] mechanism in highly polar photocycloadditions.

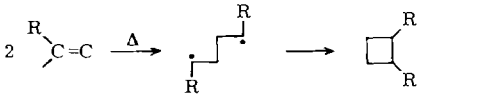
A final point remains to be made. In the theoretical discussion, we have assumed an unsymmetric pseudodiradical geometry because it corresponds to the most general case in terms of configuration mixing. However, in modestly [2+2] photocycloadditions involving a carbonyl group the pseudodiradical geometry can be either of the symmetric or unsymmetric type.



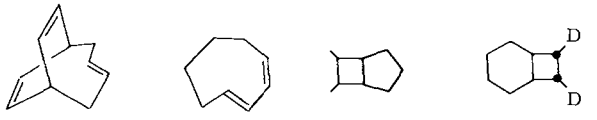
Now, B_1 is the product of the mixing of configurations C_n^*D and $C^{\ominus}D^{\oplus}$. The matrix element of these two configurations is greater for the symmetric geometry and, hence, B_1 corresponding to such geometry has lower energy than B_1 corresponding to the unsymmetric geometry. Consequently, in modestly polar [2+2] photocycloadditions involving a carbonyl group, the "diradical" involves appreciable three center bonding.

3.3. Applications

We are now prepared to compare our predictions with actual experimental data. Thermal [2+2] cyclodimerizations (AA cycloadditions) are examples of [2+2] cycloadditions which fall in the extreme nonpolar end of the reactivity spectrum. In such reactions, the concerted [2s+2a] pathway is minimally stabilized, while the [2s+2s] concerted pathway is not stabilized, and, as a result, a two-step reaction mechanism becomes highly probable. The regioselectivity of [2+2] thermal cyclodimerizations is consistent with a diradical mechanism and not a concerted [2s+2a] mechanism[41]. A diradical mechanism leads in most cases, but not all, to head-to-head cyclobutane derivatives and a [2s+2a] mechanism to head-to-tail cyclobutane products. Hence, the observed head-to-head regioselectivity of [2+2] thermal cyclodimerizations argues for a diradical mechanism.



The stereochemistry of thermal [2+2] cyclodimerizations has been extensively studied. The thermal [2+2] cyclodimerization of the bicyclic *(17)* has been thought to occur in a concerted [2s+2a] manner[42]. However, the thermal [2+2] cyclodimerization of *(18)* has been studied by *Padwa et al.* and been found to proceed *via* the intermediacy of diradicals[43,44].

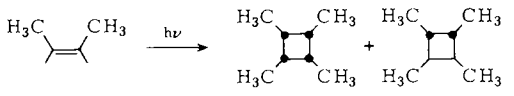


(17) *(18)* *(19)* *(20)*

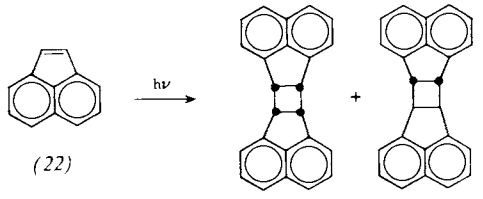
The stereochemistry of extremely nonpolar [2+2] cycloadditions and cycloreversions has been studied by various workers; in most cases the results are consistent with a diradical mechanism. Thus, the decomposition of the *cis* and *trans* isomers of 6,7-dimethylbicyclo[3.2.0]heptane *(19)* occurs *via* a diradical mechanism[45] and the experimental results are quite similar to those obtained for the decomposition of the *cis* and *trans* isomers of 1,2-dimethylcyclobutane[46]. The cycloaddition of tetrafluoroethylene and 1,2-dideuterioethylene was found to yield cyclobutane products and the observed stereochemistry is consistent with a diradical mechanism[47]. Finally, the pyrolysis of *(20)* yields *trans*-1,2-dideuterioethylene as the major isomer and the proportion of the *trans* isomer formed is larger than would be expected in a thermodynamically controlled reaction[48]. These last results indicate that a [2s+2a] concerted mechanism and a stepwise mechanism involving diradical intermediates are probably in competition.

In addition, it should be mentioned that the kinetic parameters of cyclobutane decomposition were shown to be both qualitatively and quantitatively consistent with the diradical mechanism[49,50]. In short, it appears that regiochemical, stereochemical and kinetic criteria favor a two-step mechanism for most thermal [2+2] cycloadditions which are found at the *extremely* nonpolar end of the reactivity spectrum.

Photochemical [2+2] cycloadimerizations which occur *via* the first excited singlet state of the reaction complex are expected to be [2s+2s] stereoselective. Available experimental results confirm these predictions[51-53]. The reactions of *(21)* and *(22)* are examples.



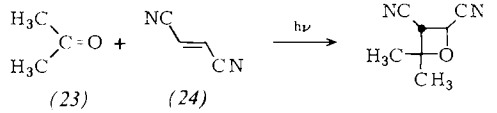
(21) major product



(22) major product

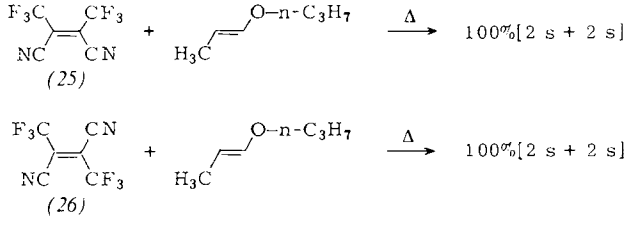
It is very important to note that the regioselectivity of these two photodimerizations has been shown to be consistent with a concerted [2s+2s] mechanism[41]. A large number of [2+2] photodimerizations known to yield products consistent with a concerted [2s+2s] mechanism can be found in recent reviews[54].

Nonpolar [2+2] photocycloadditions involving an excited carbonyl group are predicted to be [2s+2s] stereoselective. Experimental results, *e.g.* in the reaction of *(23)* with *(24)*, have confirmed these expectations[55].

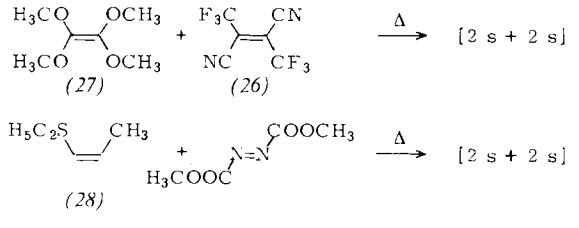


(23) (24)

Polar [2+2] cycloadditions have been studied extensively. In such reactions, both the [2s+2a] and the [2s+2s] concerted pathways are stabilized electronically but the unfavorable steric features of the [2s+2a] transition state lead to the prediction that polar [2+2] cycloadditions will occur in a concerted [2s+2s] manner. We believe that the experimental data strongly indicate that this prediction is, in most cases, correct. The reactions of *(25)* and *(26)* are examples of stereospecific [2s+2s] cycloadditions[56].



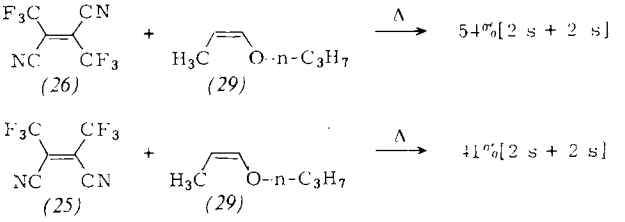
The polar cycloadditions of *(27)* and *(28)* are [2s+2s] stereospecific with respect to the stereochemically labeled acceptor or donor partner, which is a strong indication that the overall reaction is a concerted [2s+2s] process[57,58]. Many other such reactions are known[56,59].



(27) (26)

(28)

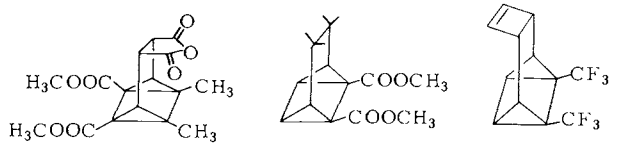
The exceptions to the rule are also interesting. For example, the following reactions of *cis-n*-propoxy-1-propene *(29)* with *(26)* and with *(25)* are nonstereospecific and the products can be thought to arise from a dipolar intermediate. However, an alternative interpretation is that the products arise from competing [2s+2s] and [2s+2a] mechanisms. The latter interpretation becomes even more credible on account of the observation that in the formal [2s+2a] products rotation has only occurred in the acceptor partner. Indeed, a dipolar intermediate would have led to rotation of either donor or acceptor partner.



(26) (29)

(25) (29)

Kinetic evidence in favor of polar [2s+2s] concerted cycloadditions is also available. Specifically, polar [2+2] cycloadditions are very facile reactions and can occur even at room temperature. The intramolecular cycloreversions of the molecules *(30)*—*(32)* have been studied and in all cases the product was the corresponding norbornadiene derivative.



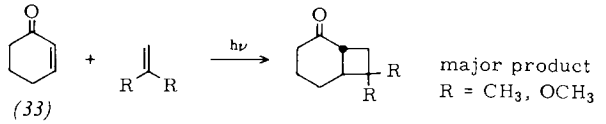
(30) (31) (32)

It was found that *(32)* decomposes slowly at 80°C[60], *(31)* has a half life of 12 min at 19°C[61], and *(30)* has a half life of 3 min at 20°C[62]. In other words, increasing polar character of the cycloreversion leads to faster decomposition rates. An even more impressive result was the determination of the kinetic parameters[62]. It was found that ΔH^{+} for the reaction of *(30)* to the norbornadiene derivative was very much lower than ΔH^{+} for the reaction of quadricyclane to norbornadiene. Yet more impressive was the finding that ΔS^{+} for reaction of *(30)* was very similar to ΔS^{+} for the rearrangement of *cis*-divinylcyclobutane, a concerted reaction. Other examples of facile intramolecular polar [2+2] cycloadditions can be found in the literature[62].

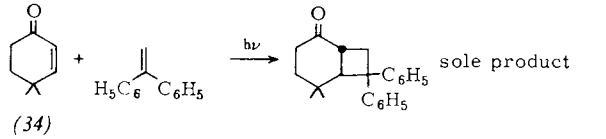
In the past, the stereoselectivity of thermal [2+2] cycloadditions has been rationalized by assuming formation of a diradical or dipolar intermediate. By invoking such intermediates, one can rationalize any set of chemical data. On the other hand, the diradical or dipolar intermediate concept is uniquely poor in leading to predictions. In short, we believe that the wide acceptance of such molecular species as intermediates in thermal [2+2] cycloadditions has been a matter of convenience. In general, diradical intermediates are expected to be important in extremely nonpolar cases where *both one electron and two electron configuration mixing is poor*. Semipolar and polar cycloadditions can involve appreciable pericyclic bonding at the transition state and may not be two-step reac-

tions in the classical sense. The stereoselectivity of [2+2] cycloadditions of substituted butadienes to substituted olefins can be explained by a predominant concerted [2s+2a] mechanism[110]. Such reactions are located near the middle of the cycloaddition reactivity spectrum and stabilization of the [2s+2a] transition state can be appreciable. The stereospecificity of polar [2+2] cycloadditions can be explained by a predominant [2s+2s] mechanism.

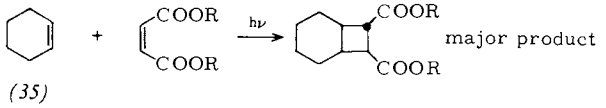
Polar [2+2] photocycloadditions *occurring via the first excited singlet state of the reaction complex* are expected to be [2s+2a] stereoselective, unless steric interactions raise the energy of the lowest excited [2s+2a] pericyclic state. In general, polar [2s+2a] photocycloadditions are expected when at least one partner is a *cis*-disubstituted ethylene molecule. In such cases, the two cycloaddends can approach each other in a [2s+2a] manner and significant orbital overlap can take place. Furthermore, antarafacial union can be facilitated by a twisted geometry of the photoexcited partner, The reactions of the cyclohexenes *(33)—(35)* are examples of polar stereoselective [2s+2a] photocycloadditions[63-66].



(33)

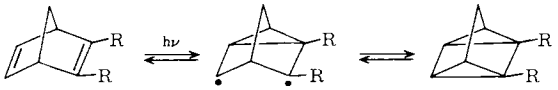


(34)

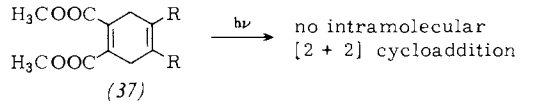


(35)

A most interesting situation obtains when one attempts a polar [2+2] photocycloaddition which is sterically prohibited from occurring in a [2s+2a] manner. In the systems *(36)* and *(37)* intramolecular [2+2] photocycloaddition can only occur in the lowest excited [2s+2s] pericyclic state which, as we have seen, *involves only weak pericyclic bonding because of poor configuration mixing*. As a result, the intramolecular [2+2] photocycloaddition may either occur *via* a stepwise mechanism or not at all. These expectations have been confirmed by experiment[67].



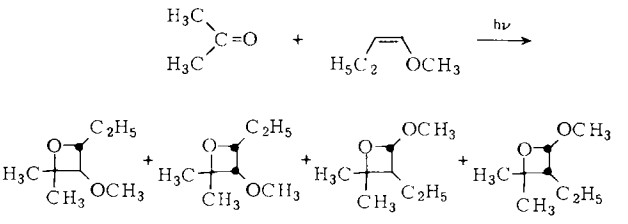
(36)



(37)

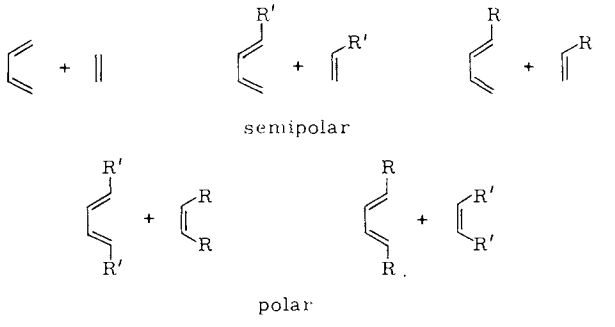
R = C_6H_5

Polar photocycloadditions involving the carbonyl group are also known. Modestly polar [2+2] photocycloadditions of carbonyl groups are predicted to occur *via* a "diradical" mechanism. This expectation has been confirmed by *Turro*[68]. On the other hand, extremely polar [2+2] photocycloadditions of carbonyl groups are predicted to be [2s+2a] stereoselective, but such reactions have not yet been studied.



4. Intermolecular [4+2] Cycloadditions

In the case of intermolecular [2+2] cycloadditions, we can distinguish nonpolar (AD) and polar (AX) reactions; the intermolecular [4+2] cycloadditions can be divided into semipolar (AM) and polar (AX) reactions. In the typical examples of semipolar and polar [4+2] cycloadditions shown below, R' is the donor and R the acceptor substituent.



The stereoselectivity of semipolar and polar [4+2] cycloadditions is analyzed in the same way as the stereoselectivity of nonpolar and polar [2+2] cycloadditions. Specifically, one of the cycloaddends is defined as the donor and the other as the acceptor, the basis set configurations and the corresponding Slater determinant wavefunctions are constructed, and the general interaction matrix is built. Expansion of the MO integrals into AO integrals leads to the interaction matrices for [s+s] and [s+a] union and ultimately to the construction of the corresponding electron states. Figure 14 shows the electronic states for semipolar [4s+2s] and [4s+2a] union and Fig. 15 the electronic states for polar [4s+2s] and [4s+2a] union. The effect of asymmetry induced configuration mixing is included in these diagrams. One is led to the following conclusions:

a) A concerted semipolar [4+2] cycloaddition will proceed thermally in a [4s+2s] manner because the lowest electronic state S_0 involves pericyclic bonding and is of lower energy than the lowest electronic state A_0 (which is not pericyclic). The electronic stabilization of the [4s+2s] and [4s+2a] transition state complexes due to configuration interaction are:

$$SE(4s+2s) = E(S_0) - E(DA) > 0$$
$$SE(4s+2a) = E(A_0) - E(DA) = 0$$

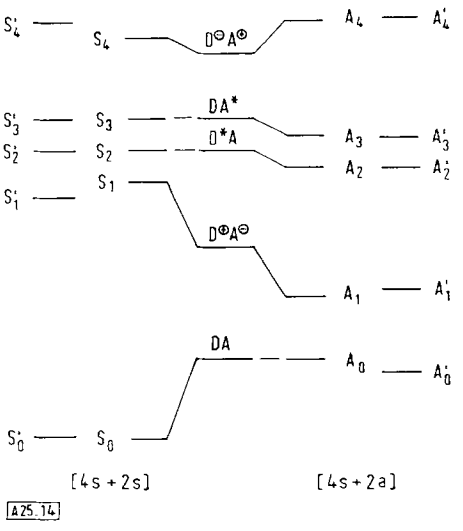


Fig. 14. Configuration interaction diagram for a semipolar [4+2] cycloaddition. The S and A states refer to symmetrical cases and the S' and A' states to unsymmetrical cases.

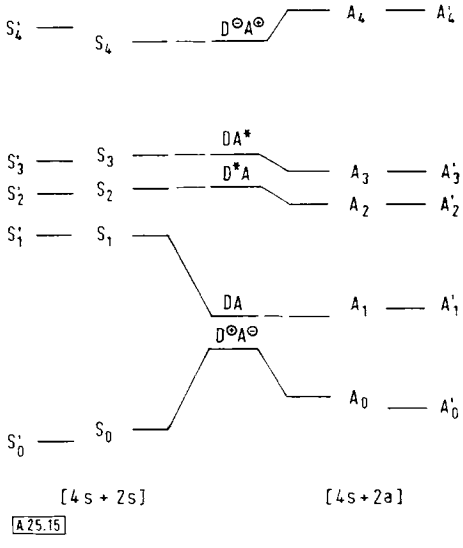


Fig. 15. Configuration interaction diagram for polar [4+2] cycloaddition. The S and A states refer to symmetrical cases and the S' and A' states to unsymmetrical cases.

The magnitude of the electronic stabilization of the [4s+2s] transition state complex is moderate and there is no steric destabilization. Hence, a concerted [4s+2s] mechanism can compete effectively with a stepwise mechanism involving diradical intermediates. Nonetheless, we emphasize that the stabilization $SE(4s+2s)$ is at a minimum at the extreme semipolar end of the [4+2] cycloaddition reactivity spectrum.

b) A concerted semipolar [4+2] cycloaddition will proceed photochemically in a [4s+2a] manner because A_1 has lower energy than S_1 and both states involve pericyclic bonding. Whenever steric destabilization of the excited electronic states of the [4s+2a] transition state complex is small, A_1 will have lower energy than S_1. It should be pointed out, however, that such photochemical reactions will be dominated by the competing [2s+2s] photochemical reaction involving one olefinic bond of the diene and one olefinic bond of the dienophile. Finally, we note that A_1 has excimeric character and involves strong pericyclic bonding and S_1 has charge transfer character and involves weak pericyclic bonding.

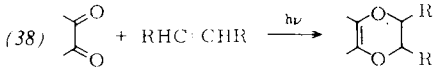
c) A concerted polar [4+2] cycloaddition will proceed thermally in a [4s+2s] manner because both S_0 and A_0 electronic states involve pericyclic bonding. The electronic stabilization of the [2s+2s] and [4s+2a] transition state complexes due to configuration interaction are

$$SE(4s+2s) = E(S_0) - E(D\ A\ ) > 0$$
$$SE(4s+2a) = E(A_0) - E(D\ A\ ) > 0$$

The magnitude of the electronic stabilization of the [4s+2s] transition state complex is greater than the electronic stabilization of the [4s+2a] transition state complex due to configuration interaction. Furthermore, steric effects favor the former over the latter to a great extent. Hence, thermal polar [4+2] cycloadditions are expected to occur in a concerted [4s+2s] manner on account of strong electronic stabilization and favorable geometry. A stepwise mechanism is considered unlikely because the overall stabilization of the [4s+2s] transition state complex is at a maximum at the extreme polar end of the [4+2] cycloaddition reactivity spectrum.

d) A concerted polar [4+2] cycloaddition will proceed photochemically in a [4s+2s] manner because the first excited electronic state S_1 involves pericyclic bonding, while the first excited electronic state A_1 does not; A_1 is a nonbonding state. Furthermore, S_1, the lowest excited state involving [4s+2s] pericyclic bonding, has lower energy than A_2, the lowest excited state involving [4s+2a] pericyclic bonding. Steric effects can only accentuate the energy difference between S_1 and A_2. Finally, we note that S_1 has charge transfer character and involves strong pericyclic bonding, while A_2 has excimer character and involves weak pericyclic bonding.

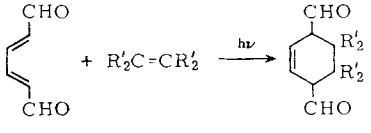
An important class of semipolar [4+2] photocycloadditions involves the electronically excited carbonyl group of diketones



such as *(38)*. These reactions can be analyzed in the same manner as were the nonpolar [2+2] photocycloadditions involving an excited carbonyl group. The conclusion is that such reactions will tend to be [4s+2a] stereoselective; however, the alternative mode of [2s+2s] union will probably dominate.

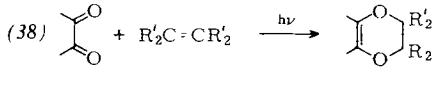
There are two classes of polar [4+2] photocycloadditions which are of special interest to the organic chemist:

a) Polar [4+2] photocycloadditions involving nπ* excitation of one cycloaddend:



R' = $N(CH_3)_2$, OCH_3, etc.

b) Polar [4+2] cycloadditions involving an excited carbonyl group:



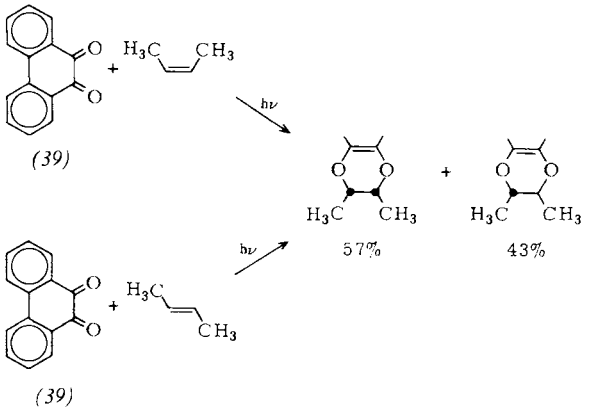
R' = $N(CH_3)_2$, OCH_3, etc.

By following the same analysis as in the case of the corresponding [2+2] photocycloadditions, we conclude that a polar photocycloaddition involving $n\pi^*$ excitation of one cycloaddend will be [4s+2s] stereoselective. On the other hand, a modestly polar photocycloaddition involving an $n\pi^*$ excited carbonyl group will occur *via* a diradical mechanism, while a very polar reaction of the same type will be [4s+2s] stereoselective[69].

In thermal semipolar [4+2] cycloadditions, the concerted pathway *via* a [4s+2s] mechanism is electronically stabilized and the concerted [4s+2a] pathway is not. Hence, these reactions are expected to be concerted because the [4s+2s] pathway is sterically unencumbered. However, the electronic stabilization of the [4s+2s] pathway is only modest in the case of semipolar [4+2] cycloadditions. As a result, the transition state for the reaction can be highly unsymmetrical and almost resemble a diradical. These arguments are supported by experimental evidence[71] and theoretical considerations. Thus, it has been found that the observed regioselectivity of semipolar [4+2] cycloadditions is consistent with a highly unsymmetrical, diradical-like transition state[41]. Furthermore, kinetic analysis has implicated a diradical mechanism in certain semipolar [4+2] cycloadditions[70]. An interesting observation: the stereochemistry of extremely semipolar [4+2] cycloadditions has not yet been studied. Such experiments could provide important information about the mechanism of these reactions.

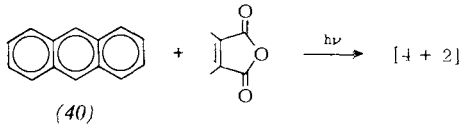
Semipolar [4+2] photocycloadditions occurring *via* the first excited singlet state of the reaction complex are expected to be [4s+2a] stereoselective. However, this sterically unfavorable reaction will probably be dominated by the sterically unhindered [2s+2s] reaction. The mechanism of nonpolar [4+2] photocycloadditions is difficult to study.

Semipolar [4+2] photocycloadditions involving carbonyl groups are likewise difficult to study. The same problem is met with in these reactions as in the corresponding reactions of normal unsaturated systems: the [2s+2s] reaction dominates over the [4s+2a] photocycloaddition. Modestly polar [4+2] reactions of this type are predicted to occur by a pseudodiradical mechanism. Typical experimental results for reactions of the latter type—*e.g.* the reaction of phenanthraquinone *(39)* with *cis*- and *trans*-2-butene—are given below[72].



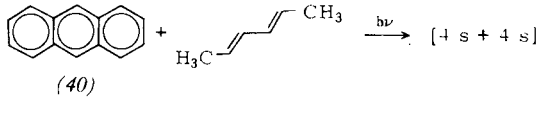
(39)

The kinetics[10,73], regiochemistry[41,74] and stereochemistry[75] of polar, thermal [4+2] cycloadditions are consistent with a concerted [4s+2s] mechanism. These reactions have been studied extensively and there is common agreement that most of them are concerted reactions. Polar [4+2] photocycloadditions occurring *via* the first excited state of the reaction complex are expected to be [4s+2s] stereoselective. Such reactions have been known for a long time[76].

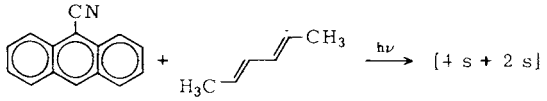


(40)

A most impressive example of a [4s+2s] stereoselective polar [4+2] photocycloaddition was recently reported by *Yang et al.*[77]. Two typical findings from their investigations on anthracene *(40)* and 9-anthracenecarbonitrile *(41)* are shown below. It is clear that increasing the polarity of the reactants shifts the stereoselectivity from [4s+4s] to [4s+2s]. Other stereoselective [4s+2s] polar photocycloadditions are also known to occur[78].

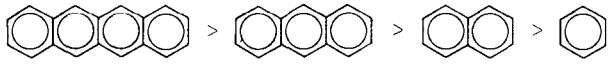


(40)



(41)

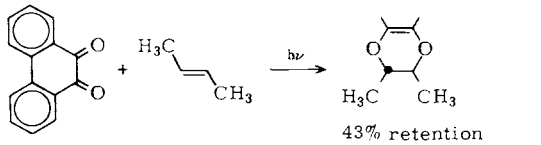
It is interesting to point out that Hückel calculations as well as experimental ionization potentials (I.P.) and electron affinities[79] indicate that the electron donating and electron accepting ability of polynuclear arenes varies in the order:



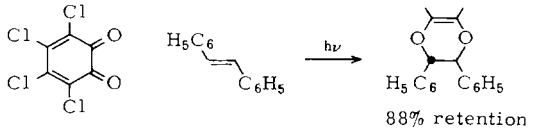
I. P. [eV]	7.15	7.55–7.66	8.12	9.25

It is known that benzene, a poor donor, reacts photochemically with maleic anhydride to yield a [2+2] photoadduct[80], while, as we have already seen, anthracene, a good donor, reacts photochemically with maleic anhydride to yield a [4+2] photoadduct. This contrasting behavior can be readily explained in terms of our analysis.

Highly polar [4+2] cycloadditions involving the carbonyl group are known to be [4s+2s] stereoselective. The results obtained with phenanthraquinone *(39)* and tetrachloro-*o*-



(39)



(42)

benzoquinone *(42)* show that an increase in the electron donating ability of one partner and the electron accepting ability of the other is paralleled by an increase in the [4s+2s] stereoselectivity of the reaction[81,82].

5. Electrocyclic Reactions

As we have discussed already, electrocyclic ring closures are concerted intramolecular cycloadditions and electrocyclic ring openings are concerted intramolecular cycloreversions. In general, an intramolecular [2s+2a] cycloaddition or cycloreversion corresponds to a conrotatory ring closure or ring opening and an intramolecular [2s+2s] cycloaddition or cycloreversion corresponds to a disrotatory ring closure or ring opening. Accordingly, one expects that the stereoselectivity patterns of electrocyclic reactions will resemble the stereoselectivity patterns of concerted intermolecular cycloadditions. In view of these expected similarities, we have chosen to develop the one electron configuration interaction theory of electrocyclic reactions by omitting details which can be found in Section 3.

We first examine the nonpolar ring closure (AD) of butadiene *(43)*.



(43)

This reaction is formally equivalent to an intramolecular [2+2] cycloaddition of *(1)* and *(2)*, where *(1)* is assumed to be the donor partner and *(2)* the acceptor partner (see Section 3.1). Unlike intermolecular [2+2] cycloadditions, there can only be unequal bond making between C^2 and C^5 and between C^3 and C^6 in the transition state. The one electron Hamiltonian, the basis set configurations, and the corresponding Slater determinant wave functions, are the same as in the case of the intermolecular nonpolar cycloaddition of *(1)* and *(2)*. However, expansion of the MO integrals of the general interaction matrix into AO integrals yields different results because of the unequal bonding. Thus, in the case of disrotatory ring closure, the MO integrals become:

$$\langle\phi_3|H'|\psi_2\rangle = C_{32}C_{25}(\beta-\gamma)$$
$$\langle\phi_4|H'|\psi_1\rangle = C_{42}C_{15}(\beta-\gamma)$$
$$\langle\phi_4|H'|\psi_2\rangle = C_{42}C_{25}(\beta+\gamma)$$
$$\langle\phi_3|H'|\psi_1\rangle = C_{32}C_{15}(\beta+\gamma)$$

where

$$\beta = \langle p_2|H'|p_5\rangle \quad |\beta|>|\gamma|$$
$$\gamma = \langle p_3|H'|p_6\rangle$$

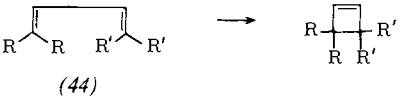
In the case of conrotatory ring closure, *i.e.* intramolecular [2s+2a] cycloaddition, the MO integrals become:

$$\langle\phi_3|H'|\psi_2\rangle = C_{32}C_{25}(\beta+\gamma)$$
$$\langle\phi_4|H'|\psi_1\rangle = C_{42}C_{15}(\beta+\gamma)$$
$$\langle\phi_4|H'|\psi_2\rangle = C_{42}C_{25}(\beta-\gamma)$$
$$\langle\phi_3|H'|\psi_1\rangle = C_{32}C_{25}(\beta-\gamma)$$

Construction of the interaction matrices for disrotatory and conrotatory ring closure leads to the configuration interaction diagrams which show how the electronic states for the two modes of ring closure are derived from the basis set configurations. These diagrams are qualitatively similar to those for unsymmetric intermolecular [2+2] nonpolar cycloadditions (Fig. 4). In this case, A'_n are the electronic states for conrotation and S'_n are the electronic states for disrotation. In the absence of special constraints, steric effects are comparable for disrotation and conrotation. Hence, the relative energy of the electronic states corresponding to disrotation and conrotation can be assessed from consideration of the configuration interaction diagrams alone. An examination of Fig. 4 reveals that thermal ring closure of a nonpolar butadiene will occur in a conrotatory manner because the lowest electronic state A'_0 involves pericyclic bonding and has a much lower energy than the lowest electronic state S'_0. In other words, the conrotatory transition state is stabilized by configuration interaction to a great extent whereas stabilization of the disrotatory transition state is negligibly small.

In contrast, concerted ring closure of a nonpolar butadiene will occur photochemically in a disrotatory manner because the first excited electronic state S'_1 has lower energy than the first electronic state A'_1 although both states involve pericyclic bonding. It is important to note that the first excited state for disrotation has excimer character and involves strong pericyclic bonding, while the first excited state for conrotation has charge transfer character and involves weak pericyclic bonding.

We now proceed to examine the polar (AX) ring closure of butadienes of the type *(44)*. This reaction is formally equivalent to an intramolecular [2+2] cycloaddition. Again, unlike intermolecular [2+2] cycloadditions, there can only be unequal bond making between the uniting centers. Our analysis proceeds in exactly the same manner as in the case of ring closure of nonpolar butadiene. The basis set configurations for the ring closure transition state are constructed in the usual manner; the corresponding wavefunctions are written as Slater determinant wave functions. Subsequent expansion of the MO integrals of the general interaction matrix into AO integrals leads to the interaction matrices for disrotatory and conrotatory ring closure. The configuration interaction diagrams are qualitatively similar to those for unsymmetric intermolecular [2+2] polar cycloadditions (Fig. 6). In this case, A'_n are the electronic states for conrotation and S'_n are those for disrotation. Unlike the case of nonpolar ring closure, both A'_0 and S'_0 electronic states involve pericyclic bonding; A'_0 has lower energy than S'_0. Thus, we conclude that, in the absence of steric constraints, A'_0 will remain lower in energy than S'_0 and the ring closure will proceed in a conrotatory manner. In other words, both disrotation and conrotation transition states are stabilized by configuration interaction, but, in the absence of steric constraints, the conrotation transition state will have lower energy than the disrotation transition state, at least in most cases. A'_1 is, however, pericyclic whereas



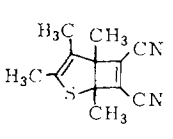
(44)

R = CN, CHO, $COOCH_3$, etc.
R' = $N(CH_3)_2$, OCH_3, etc.

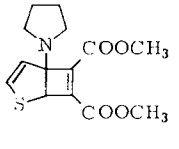
S'_1 does not involve pericyclic bonding to any substantial degree. Furthermore, A'_1, the lowest excited state involving pericyclic bonding appropriate to conrotatory ring closure, has lower energy than S'_2, the lowest excited state involving pericyclic bonding appropriate to disrotatory ring closure. Hence, a photochemical ring closure of butadiene will occur in a conrotatory manner. Again, it is important to note that the first excited state for conrotation has charge transfer character and involves strong pericyclic bonding, while the first pericyclic excited state for disrotation has excimer character and involves weak pericyclic bonding.

According to our analysis, thermal ring closures of butadienes should occur in a conrotatory fashion regardless of whether the two double bonds bear substituents of similar or opposite electronic nature. Indeed, the butadiene → cyclobutene and cyclobutene → butadiene transformations have been shown to occur in a conrotatory manner when the two reaction fragments carry identical substituents[83]. However, there have not been any studies on such systems in which the substrates bear substituents of opposite electronic nature.

While conrotation is expected to dominate over disrotation throughout the entire reactivity spectrum, both the barrier to conrotation and the barrier to disrotation decrease as the reactant becomes unsymmetrically substituted. Thus, if ring opening or ring closure is sterically constrained to occur in a disrotatory manner, asymmetric substitution of the cyclobutene or the diene will tend to reduce the activation energy for disrotation. There are many examples which indicate that these predictions are correct. Thus, it was found that *(45)* is thermally stable, whereas *(46)* opens to the seven-membered ring upon heating[84].

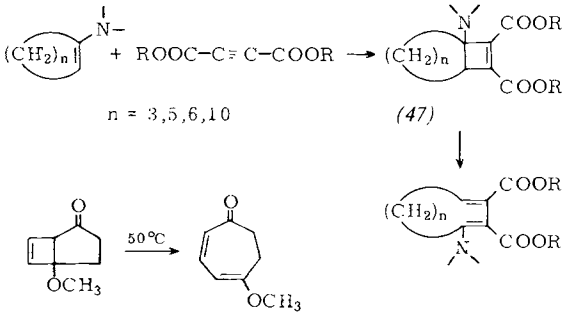


(45)



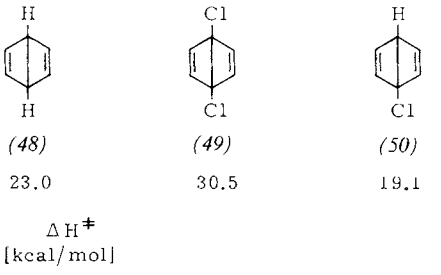
(46)

A host of reactions, which are thought to proceed *via* unsymmetrically substituted cyclobutenes, yield products with an opened cyclobutene ring. This occurs despite the fact that the cyclobutene intermediate, *e.g. (47)*, can open only by disrotation[85,86].



n = 3,5,6,10 *(47)*

Finally, a most remarkable illustration of the effect of asymmetric substitution on the barrier to disrotation has been presented by *Breslow et al.*[87]. They determined the enthalpies of activation for disrotatory ring opening of three typical Dewar-benzenes *(48)*—*(50)*.



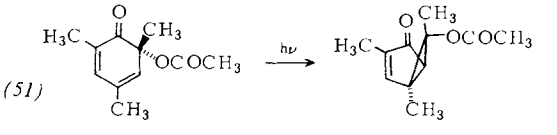
(48) *(49)* *(50)*

23.0 30.5 19.1

$\Delta H^{\neq}$ [kcal/mol]

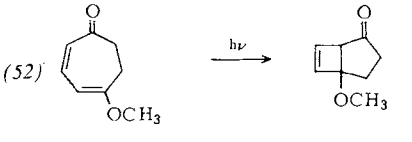
Other examples are known[88].

Photochemical ring openings and ring closures of symmetrically substituted reactants should occur in a disrotatory manner, if one assumes that the first excited state of the reacting complex is involved. Experimental evidence is in accord with these predictions[89]. The interesting prediction that photochemical ring closures and ring openings of unsymmetrically substituted reactants should occur in a conrotatory manner has not yet been tested. However, it is noteworthy that 2,4-cyclohexadienones such as *(51)*, which are constrained to undergo photochemical ring closure only by disrotation, have been found to yield no ring closure products upon irradiation[90].



(51)

The more flexible 2,4 cycloheptadienones, on the other hand, are known to yield ring closure products upon irradiation[91]. It would be very interesting to investigate whether a transient *trans* fused bicyclic product, arising from conrotatory ring closure, is at all involved in these reactions[92].



(52)

As in the case of butadiene ring closure, we can distinguish semipolar (AM) and polar (AX) hexatriene ring closures. Our configuration interaction analysis proceeds in the same manner as in the case of butadiene ring closures. The configuration interaction diagrams for semipolar conrotatory and disrotatory ring closure are similar to those in Fig. 14 and the configuration interaction diagrams for conrotatory and disrotatory polar ring closure are similar to those in Fig. 15. In both figures, A'_n correspond to the electronic states for conrotation and S'_n to the electronic states for disrotation. The following conclusions are reached:

a) A concerted semipolar hexatriene ring closure will occur thermally in a disrotatory manner because the lowest electronic state S'_0 involves pericyclic bonding and has lower energy than the lowest electronic state A'_0.

b) A concerted semipolar hexatriene ring closure will occur photochemically in a conrotatory manner because the first excited electronic state A'_1 has lower energy than the first excited electronic state S'_1 although both states involve pericyclic bonding.

c) A concerted polar hexatriene ring closure will occur thermally in a disrotatory manner because the lowest electronic state S_0' has lower energy than the lowest electronic state A_0'; both states involve pericyclic bonding.

d) A concerted polar hexatriene ring closure will occur photochemically in a disrotatory manner because S_1' involves strong pericyclic bonding but A_1' does not, *i. e.* A_1' is nearly a nonbonding state. Furthermore, S_1', the lowest excited state involving pericyclic bonding in a disrotatory mode, has lower energy than A_2', the lowest excited state involving pericyclic bonding in the conrotatory mode.

Thermal and photochemical electrocyclic reactions of symmetrically substituted hexatrienes and cyclohexadienes have been found to occur by disrotation and conrotation, respectively[93]. The effect of asymmetric substitution on the barrier to thermal conrotatory ring closure and ring opening has not been studied. The prediction that asymmetrically substituted hexatrienes and cyclohexadienes should undergo photochemical ring closure and ring opening, respectively, by disrotation has also not yet been tested.

6. Sigmatropic Shifts

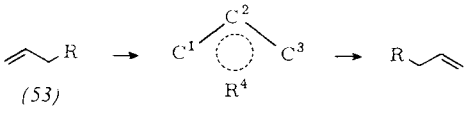
6.1. [1,3]-Shifts

We first examine the case of nonpolar (AD) [1,3] sigmatropic shifts. There can be two types:

a) Type I: nonpolar [1,3] sigmatropic shifts, where the migration framework is the donor fragment and the migrating group the acceptor fragment, but the difference in the electron donating and electron accepting ability of the two fragments is small; *i. e.* the ionization potential of the migration framework is slightly less than that of the migrating group.

b) Type II: nonpolar [1,3] sigmatropic shifts, where the migration framework is the acceptor fragment and the migrating group the donor fragment, but the difference in the electron donating and electron accepting ability of the two fragments is small; *i.e.* the ionization potential of the migration framework is slightly greater than that of the migrating group.

We shall examine in detail a type I nonpolar [1,3] sigmatropic shift.



(53)

In the reaction shown above, the migration framework in *(53)* is the allyl radical and the migrating group is the R radical. The former constitutes the donor fragment and the latter constitutes the acceptor fragment. In order to simplify the discussion, we assume that equal bond making between R and C_1 and between R and C_3 has taken place at the transition state. The one electron Hamiltonian is written as follows:

$$H = H(\text{Allyl}) + H_R + H'$$
$$H' = H_{41} + H_{43}$$

The basis set configurations for the type I nonpolar [1,3] sigmatropic shift are shown in Fig. 16 and the corresponding wavefunctions can be written as Slater determinant wavefunctions in the manner illustrated in Section 2. In this case, we have used a more extensive basis set of six zero order configurations because we deal with the special problem of the interaction of two open shell systems.

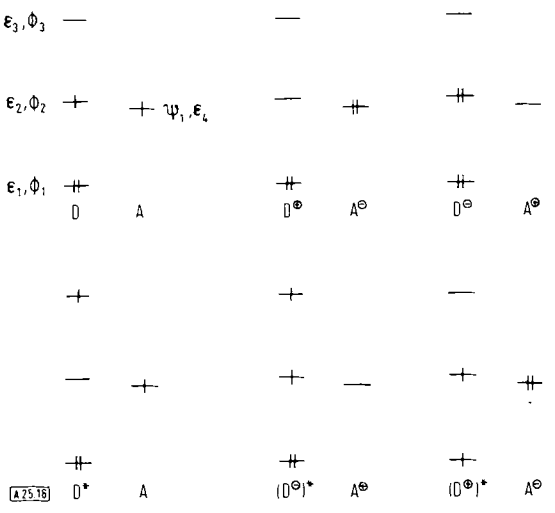


Fig. 16. Basis set configurations for a nonpolar [1,3] sigmatropic shift. D is the donor fragment and A the acceptor fragment.

In the case of the interaction of two closed shell fragments D and A, the quantity $I_D - A_A$ is satisfactorily approximated in simple Hückel theory by the energy difference between the HOMO of the donor and the LUMO of the acceptor. In contrast, in the case of the interaction of two open shell systems D and A, the quantity $I_D - A_A$ cannot be approximated by the energy difference between the singly occupied, nonbonding MOs of the two fragments. In such cases, one has to use the experimentally determined values of I_D and A_A.

The specific example of a nonpolar [1,3] sigmatropic shift of a methyl radical across an allyl radical migration framework can be used to illustrate these considerations. The various zero order configurations of the migration transition state are qualitatively similar to those in Fig. 16. The total energies of DA, $D^{\oplus}A^{\ominus}$ and $D^{\ominus}A^{\oplus}$ can be obtained by the Hückel theory by summing over all occupied one electron MOs and correcting for coulombic interactions in the case of the $D^{\ominus}A^{\ominus}$ and $D^{\ominus}A^{\oplus}$ configurations:

$$E(\text{DA}) = 2\varepsilon_1 + \varepsilon_2 + \varepsilon_4$$
$$E(\text{D}^{\ominus}\text{A}^{\ominus}) = 2\varepsilon_1 + 2\varepsilon_4 - C'$$
$$E(\text{D}^{\ominus}\text{A}^{\oplus}) = 2\varepsilon_1 + 2\varepsilon_2 - C'$$

For reasonable distances of the two fragments in the transition state, C and C' range between 3 and 6 eV. Hence, it is predicted that the two charge transfer configurations will have much lower energy than the no bond configuration. The relative stability of these configurations is predicted to be: $D^{\oplus}A^{\ominus} > D^{\ominus}A^{\oplus} > DA$.

We can now estimate the relative energies of DA, $D^{\oplus}A^{\ominus}$ and $D^{\ominus}A^{\oplus}$ by reference to experimental results, *e. g.* the ionization potentials[94] and electron affinities[95] of the methyl and allyl moieties.

$$E(\text{DA}) = 0$$
$$E(\text{D}^{\oplus}\text{A}^{\ominus}) = 8.16 - 1.1 - C$$
$$E(\text{D}^{\ominus}\text{A}^{\oplus}) = 9.84 - 2.1 - C'$$

Unlike the previous calculations and under the assumption that C and C' range between 3 and 6 eV, the relative stability of these configurations is predicted to be $DA > D^{\oplus}A^{\ominus} > D^{\ominus}A^{\oplus}$.

This latter conclusion must be the correct one, since the experimental values of the ionization potentials and electron affinities reflect interelectronic repulsive effects which are not accounted for in the simple Hückel theory. In all subsequent discussions of sigmatropic shifts, the relative energies of the zero order configurations are obtained by reference to experimental results and in accordance with equations (1)–(5).

The relative energies of the basis set configurations for nonpolar [1,3] sigmatropic shifts are shown in Fig. 17 and the general interaction matrix is shown in Scheme 4.

The πMOs of the allyl radical and the radical R are of the general form:

$$\phi_1 = C_{11}p_1 + C_{12}p_2 + C_{13}p_3$$
$$\phi_2 = C_{21}p_1 - C_{23}p_3$$
$$\phi_3 = C_{31}p_1 - C_{32}p_2 + C_{33}p_3$$

and

$$\psi_1 = p_4$$

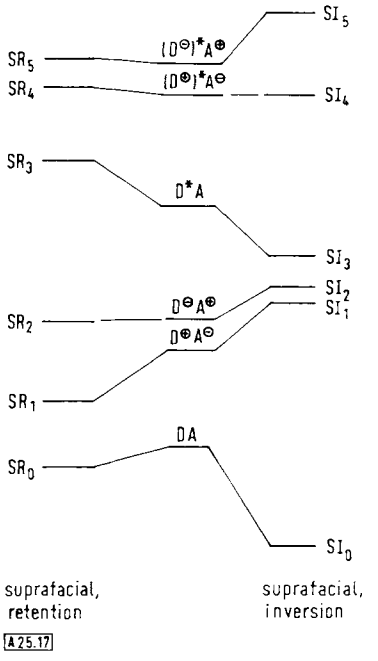


Fig. 17. Configuration interaction diagram for a nonpolar [1,3] sigmatropic shift.

The MO integrals of the general interaction matrix can be expanded into AO integrals; the interaction matrices for suprafacial migration with retention and for suprafacial migrations with inversions can be written as in Schemes 5 and 6. Examination of the interaction matrices leads to the following conclusions:

1. In the case of suprafacial migration with retention, configuration interaction produces five electronic states, SR_0, SR_1, SR_3, SR_4, SR_5 which have pericyclic character and one (SR_2) which does not. The SR_2 electronic state is nonbonding in character.

2. In the case of suprafacial migration with inversion, configuration interaction produces five electronic states, SI_0, SI_1, SI_2, SI_3, SI_5 which have pericyclic character and one (SI_4) which does not. The SI_4 electronic state is nonbonding in character.

	DA	$D^{\oplus}A^{\ominus}$	$D^{\ominus}A^{\oplus}$	D*A	$(D^{\ominus})^*A^{\oplus}$	$(D^{\oplus})^*A^{\ominus}$
DA	X					
$D^{\oplus}A^{\ominus}$	$\langle\phi_2\|H'\|\psi_1\rangle$	X				
$D^{\ominus}A^{\oplus}$	$\langle\phi_2\|H'\|\psi_1\rangle$	0	X			
D*A	0	$\langle\phi_3\|H'\|\psi_1\rangle$	0	X		
$(D^{\ominus})^*A^{\oplus}$	$\langle\phi_3\|H'\|\psi_1\rangle$	0	0	$\langle\phi_2\|H'\|\psi_1\rangle$	X	
$(D^{\oplus})^*A^{\ominus}$	$\langle\phi_1\|H'\|\psi_1\rangle$	0	0	0	0	X

Scheme 4. General interaction matrix for nonpolar [1,3] sigmatropic shifts.

	DA	$D^{\oplus}A^{\ominus}$	$D^{\ominus}A^{\oplus}$	D*A	$(D^{\ominus})^*A^{\oplus}$	$(D^{\oplus})^*A^{\ominus}$
DA	X					
$D^{\oplus}A^{\ominus}$	$C_{21}\gamma_{14} + C_{23}\gamma_{34}$	X				
$D^{\ominus}A^{\oplus}$	$C_{21}\gamma_{14} + C_{23}\gamma_{34}$	0	X			
D*A	0	0	0	X		
$(D^{\ominus})^*A^{\oplus}$	0	0	0	$C_{21}\gamma_{14} + C_{23}\gamma_{34}$	X	
$(D^{\oplus})^*A^{\ominus}$	0	0	0	0	0	X

Scheme 5. Interaction matrix for a suprafacial [1,3] sigmatropic shift with inversion.

	DA	$D^{\oplus}A^{\ominus}$	$D^{\ominus}A^{\oplus}$	D*A	$(D^{\ominus})^*A^{\oplus}$	$(D^{\oplus})^*A^{\ominus}$
DA	X					
$D^{\oplus}A^{\ominus}$	0	X				
$D^{\ominus}A^{\oplus}$	0	0	X			
D*A	0	$C_{31}\gamma'_{14} + C_{33}\gamma'_{34}$	0	X		
$(D^{\ominus})^*A^{\oplus}$	$C_{31}\gamma'_{14} + C_{33}\gamma'_{34}$		0	0	X	
$(D^{\oplus})^*A^{\ominus}$	$C_{11}\gamma'_{14} + C_{13}\gamma'_{34}$	0	0	0	0	X

Scheme 6. Interaction matrix for a suprafacial [1,3] sigmatropic shift with retention.

These considerations can be simply understood by reference to Fig. 17 which illustrates how the basis set configurations interact to form the final electronic states for the retention and inversion transition state complexes. The configuration interaction diagram of Fig. 17 is constructed under the assumption that the resonance integrals for migration with retention (γ') and migration with inversion (γ) have the same magnitude:

$$\gamma'_{14} = \gamma_{14}$$
$$\gamma'_{34} = \gamma_{34}$$

This assumption serves the dual purpose of simplifying the construction of the configuration interaction diagram and focusing our attention on the electronic factors responsible for configuration mixing. Once again, in addition to the configuration interaction diagram, we have to consider the steric features of migration with inversion in order to assess reliably the relative energy of the corresponding electronic states.

The chemical implications of Fig. 17 can be understood easily and can be stated as follows:

1. A concerted nonpolar [1,3] sigmatropic shift can proceed thermally by either of the following two stereochemical modes:

a) Inversion of configuration at the migrating group, if such a migration mode is not sterically prohibited.

b) Retention of configuration of the migrating group, if migration by inversion of the migrating group is sterically prohibited. This arises because the electronic state SI_0 and the electronic state SR_0 are pericyclic. The electronic stabilization of the two migratory modes due to configuration interaction are:

$$SE(\text{retention}) = E(SR_0) - E(D^{\oplus}A^{\ominus}) > 0$$
$$SE(\text{inversion}) = E(SI_0) - E(D^{\oplus}A^{\ominus}) > 0$$

The magnitude of the electronic stabilization of inversion is much greater than the magnitude of the electronic stabilization of retention. However, the important point is that both inversion and retention are stabilized. The [1,3] shift with inversion is, however, less sterically favored than the [1,3] shift with retention. Hence, the relative net stabilization of the two migration modes involves a very fine balance of opposing electronic and steric effects. Perhaps the most important conclusion is that, when the migration by inversion is sterically prohibited, migration by retention can proceed in a concerted manner. Using a different approach, *Berson* and *Salem* have arrived at the same conclusion[23]. Unlike the case of nonpolar intermolecular cycloadditions and electrocyclic reactions, nonpolar [1,3] sigmatropic shifts have the option of two concerted pathways. Accordingly, stepwise mechanisms are unlikely in the case of such reactions.

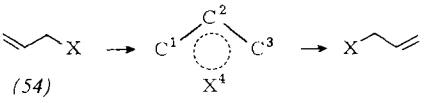
2. A concerted nonpolar [1,3] sigmatropic shift will proceed photochemically with retention of configuration of the migrating group because the lowest excited state for retention (SR_1) has lower energy than the lowest excited state for inversion (SI_1). It is important to note that SR_1 has excimer character, while SI_1 has charge transfer character.

Again, in real situations the migration framework can be unsymmetrically substituted and the migration may involve unequal bond formation at the transition state. Under these circumstances certain MO integrals can become nonzero, albeit small in magnitude. Again, calculations show that in most cases the asymmetry induced configuration mixing is small and can be neglected without altering our qualitative conclusions.

We now come to the case of polar (AX) [1,3] sigmatropic shifts. As in the previous case, there can be two types of polar [1,3] sigmatropic shifts:

a) Type I: polar [1,3] sigmatropic shifts, where the migration framework is the donor fragment and the migrating group is the acceptor fragment, and the electron donating and electron accepting ability of the two fragments differ greatly, *i.e.* the ionization potential of the migration framework is much smaller than the ionization potential of the migrating group.

b) Type II: polar [1,3] sigmatropic shifts, where the migration framework is the acceptor fragment and the migrating group is the donor fragment and the electron donating and electron accepting ability of the two fragments differ greatly, *i.e.* the ionization potential of the migration framework is much greater than the ionization potential of the migrating group. We shall examine a type I polar [1,3] sigmatropic shift in detail. In *(54)*, the migration group is the allyl radical and



(54)

the migrating group is the highly electrophilic residue X. The former is the donor and the latter is the acceptor fragment. Again, it is assumed that equal bond making between X and C_1 and between X and C_3 takes place in the transition state. Our analysis proceeds exactly in the same manner as in the case of nonpolar [1,3] sigmatropic shifts. The one electron Hamiltonian is written as follows:

$$H = H(\text{allyl}) + H_X + H'$$
$$H' = H_{41} + H_{43}$$

The basis set configurations for the [1,3] sigmatropic shift transition state complex are shown in Fig. 18; the corresponding wave functions can be written as Slater determinants. The relative energies of the basis set configurations are shown in Fig. 19. The situation is quite different from that encountered in the case of nonpolar [1,3] sigmatropic shifts. The reason

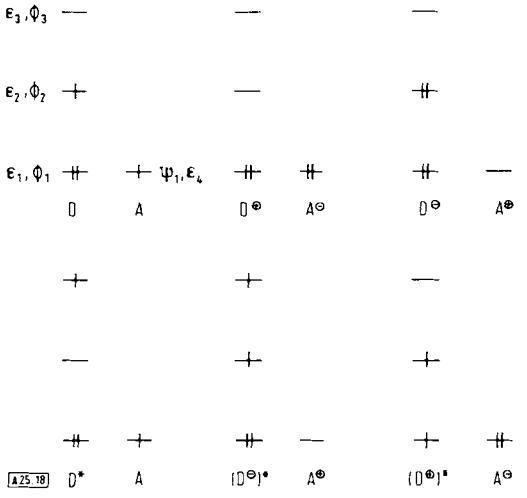


Fig. 18. Basis set configurations for a polar [1,3] sigmatropic shift. D is the donor fragment and A the acceptor fragment.

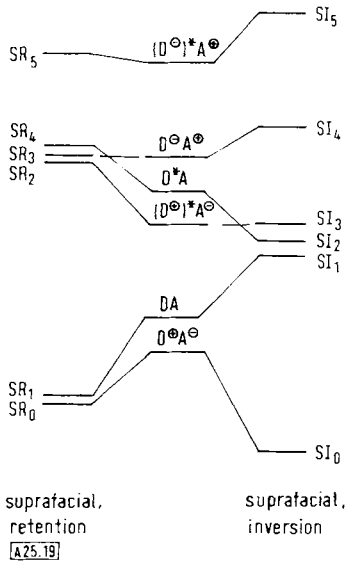


Fig. 19. Configuration interaction diagram for a polar [1,3] sigmatropic shift.

for this is as follows: on going from a nonpolar to a polar sigmatropic shift the energies of the charge transfer configurations $D^{\oplus}A^{\ominus}$ and $(D^{\oplus})^*A^{\ominus}$ progressively diminish, whereas the energies of the charge transfer configurations $D^{\ominus}A^{\oplus}$ and $(D^{\ominus})^*A^{\oplus}$ progressively increase.

We can now examine how the basis set configurations interact in order to form electronic states. We can construct the general interaction matrix, expand the MO integrals into AO integrals, and arrive at the interaction matrices for migration with retention and migration with inversion. The resultant electronic states are shown in Fig. 19. It can be seen that all states except SR_3 and SI_1 involve pericyclic bonding. The following conclusions can be drawn:

1. Polar [1,3] sigmatropic shifts can proceed thermally by retention of configuration of the migrating group. This arises because both the SR_0 and SI_0 electronic states involve pericyclic bonding. Furthermore, the electronic stabilization of the two migratory modes due to configuration interaction are:

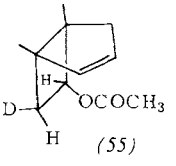
$$SE(\text{Retention}) = E(SR_0) - E(D^{\oplus}A^{\ominus}) > 0$$
$$SE(\text{Inversion}) = E(SI_0) - E(D^{\oplus}A^{\ominus}) > 0$$

As in the case of nonpolar [1,3] sigmatropic shifts, the electronic stabilization of migration by retention cannot be all that extensive. Now, even in the absence of special steric constraints, inversion is sterically destabilized relative to migration by retention. As a result, in polar [1,3] sigmatropic shifts the concerted migration by retention can dominate concerted migration by inversion. The availability of two concerted pathways makes a stepwise mechanism unlikely.

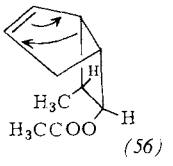
2. A concerted polar [1,3] sigmatropic shift will proceed photochemically with inversion of configuration of the migrating group if SR_0 and SR_1 are degenerate or almost degenerate, since the lowest excited state for concerted migration with inversion (SI_1) has lower energy than the lowest excited state for concerted migration with retention (SR_2). If SR_0 and SR_1 are not degenerate, however, a polar [1,3] sigmatropic shift will proceed photochemically with retention, since SR_1 will have a lower energy than SI_1. It is important to note that in photochemical polar [1,3] sigmatropic shifts, the lowest possible excited state for concerted migration with retention (SR_1) has excimer character, while the lowest possible excited state for concerted migration with inversion (SI_1) has charge transfer character.

Once more, additional configuration mixing can take place when the migration framework is unsymmetrically substituted or there is unequal bond making in the transition state. The effect is small, however, and does not influence our qualitative conclusions.

In the case of thermal nonpolar [1,3] sigmatropic shifts, both the retention and inversion concerted pathways are stabilized, the latter, however, to a greater extent than the former. Hence, in the absence of steric prohibitions, one expects that the inversion pathway can dominate. Experimental findings are consistent with this expectation. Indeed, thermolysis of compound *(55)* has provided an example of a suprafacial sigmatropic shift proceeding by inversion[96].



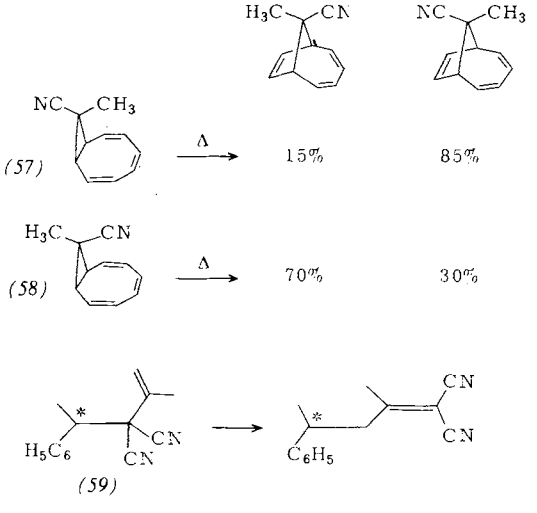
(55)



(56)

On the other hand, when migration by inversion is sterically prohibited, the reaction can occur by retention of the migrating center and still be concerted. Such examples [cf. *(56)*] are now known[97].

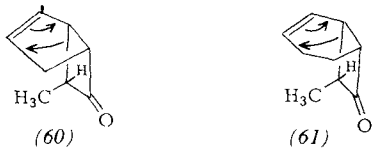
Photochemical nonpolar [1,3] sigmatropic shifts are predicted to occur by retention. However, if such a reaction mode is made sterically unfavorable, migration can occur *via* the higher electronic state by inversion. Obviously, in most cases, retention is sterically favored over inversion. In the case of thermal polar [1,3] sigmatropic shifts, both the retention and inversion concerted pathways are stabilized. However, due to a combination of electronic and steric effects, the former can be stabilized more than the latter. Thus, in the absence of steric prohibition of migration by inversion, one expects that the retention pathway can even dominate; and this has been found to be the case experimentally[98,99]. Examples are the reactions of *(57)*—*(59)*.



(59)

Of course, the same results are expected when the inversion pathway is sterically blocked. Some of the examples described by *Berson et al.* of concerted [1,3] sigmatropic shifts that

proceed by retention can be regarded as moderately polar sigmatropic shifts; such systems are, *e.g.* *(60)* and *(61)*[100].



(60) *(61)*

An important point remains to be explained. In the case of nonpolar [1,3] sigmatropic shifts both our configuration interaction approach and the subjacent orbital control one-configuration analysis predict that suprafacial migration by retention is stabilized. On the other hand, in the case of polar [1,3] sigmatropic shifts configuration interaction stabilizes suprafacial migration by retention but the subjacent orbital control effect is most likely nonexistent. The difference in the nonpolar and polar sigmatropic shifts in terms of subjacent orbital control can be understood by reference to the two interaction diagrams shown in Fig. 20. In the case of nonpolar shifts, orbital interactions lead to a pericyclic complex, whereas in the case of polar shifts they lead to an ion pair.

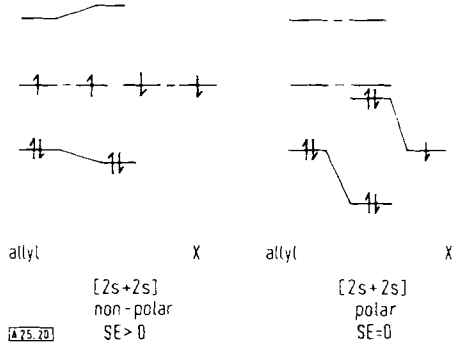
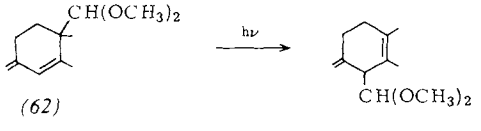


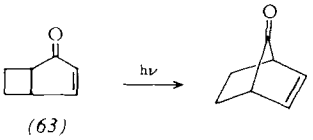
Fig. 20. Orbital interactions for nonpolar and polar [1,3] shifts.

Photochemical polar [1,3] sigmatropic shifts proceed either with inversion or with retention. Intramolecular polar [1,3] sigmatropic shifts—*e.g.* in *(62)*—have been observed photochemically but their stereochemistry is unknown[101,102].



(62)

Cookson has reported a photochemical polar [1,3] sigmatropic shift which proceeds with retention[102], while the following reaction of *(63)* was found to be nonstereoselective; a diradical mechanism was proposed[103].



(63)

In the latter reaction, nonstereoselectivity may reflect competing concerted mechanisms *via* SR_2 (or SR_1) and SI_1. Additional investigations of these reactions may clarify the situation.

6.2. [1,5] Shifts

We now turn our attention to [1,5] sigmatropic shifts. As in the case of [1,3] sigmatropic shifts, we can have two types of nonpolar and two types of polar rearrangements. We can analyze the case of nonpolar and polar [1,5] sigmatropic shifts where the migration framework is the donor and the migrating group is the acceptor fragment in the same manner in which we analyzed the [1,3] nonpolar and polar [1,3] sigmatropic shifts of the same type. The electronic states for nonpolar [1,5] sigmatropic shifts occurring by inversion and retention are shown in Fig. 21. Similarly, the electronic states for polar [1,5] sigmatropic shifts occurring by inversion and retention are shown in Fig. 22. Examination of these figures leads to the following conclusions:

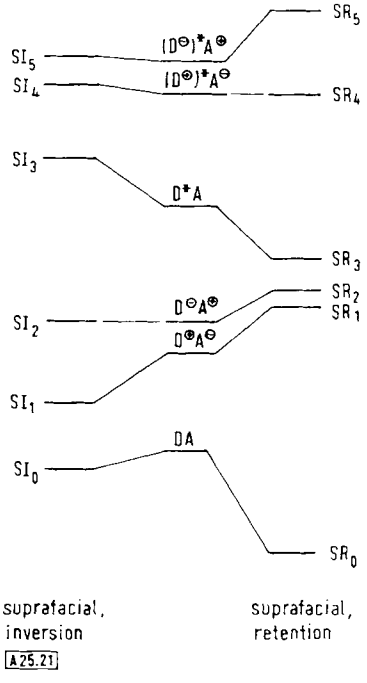


Fig. 21. Configuration interaction diagram for a nonpolar [1,5] sigmatropic shift.

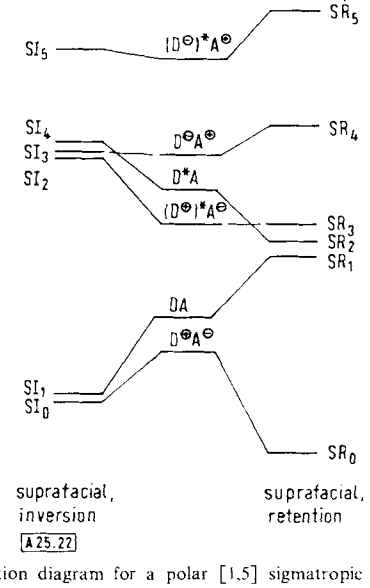


Fig. 22. Configuration interaction diagram for a polar [1,5] sigmatropic shift.

a) A concerted nonpolar [1,5] sigmatropic shift will proceed thermally by retention because the electronic state SR_0 involves pericyclic bonding and has much lower energy than the electronic state SI_0 which also involves pericyclic bonding. The electronic stabilization of the retention and inversion transition state complexes due to configuration interaction are:

$$S\,E(\text{Retention}) = E(SR_0) - E(D^{\oplus}A^{\ominus}) > 0$$
$$S\,E(\text{Inversion}) = E(SI_0) - E(D^{\oplus}A^{\ominus}) > 0$$

The electronic stabilization of retention is large and there is no steric destabilization. On the other hand, the electronic

$$CH_3\text{-}CH{=}CH\text{-}CH{=}CH_2$$

stabilization of inversion is small and there is steric destabilization. Hence, migration by retention is expected to dominate over the alternative concerted mechanism or any stepwise mechanism.

b) A concerted nonpolar [1,5] sigmatropic shift will proceed photochemically by inversion because the lowest excited state for concerted migration by inversion (SI_1) has lower energy than the lowest excited state for concerted migration by retention (SR_1).

c) A concerted polar [1,5] sigmatropic shift will proceed thermally by retention because SI_0 and SR_0 involve pericyclic bonding. The electronic stabilization of the two migration modes due to configuration interaction are:

$$S\,E(\text{Retention}) = E(SR_0) - E(D^{\oplus}A^{\ominus}) > 0$$
$$S\,E(\text{Inversion}) = E(SI_0) - E(D^{\oplus}A^{\ominus}) > 0$$

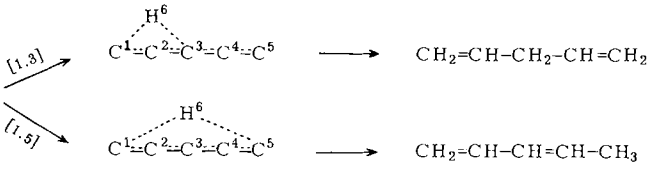
Now, the reaction path with retention is electronically and sterically stabilized to a large extent relative to that with inversion. Hence, electronic and steric factors favor concerted migration by retention over concerted migration by inversion.

d) A concerted polar [1,5] sigmatropic shift will proceed photochemically by retention if SI_0 and SI_1 are degenerate or almost degenerate, because the lowest excited state for concerted migration by retention (SR_1) has lower energy than the lowest excited state for concerted migration by inversion (SI_2). If SI_0 and SI_1 are not degenerate then rearrangement with inversion results.

7. Hydrogen Shifts

Sigmatropic hydrogen shifts are nonpolar sigmatropic shifts where hydrogen uses its 1s orbital in the course of the migration. A [1,3] hydrogen sigmatropic shift can be analyzed exactly like a nonpolar carbon shift. The migration framework is the allyl residue and the migrating group is the hydrogen atom. If we assume that only a suprafacial migration is a viable possibility, we are led to the conclusion that a thermal suprafacial shift is stabilized to a small degree by configuration interaction and that a manifold of excited, strongly pericyclic states exist *via* which a photochemical suprafacial shift can proceed. Both thermal and photochemical [1,3] hydrogen shifts are known and one can reliably assume that such reactions are concerted.

We now come to the case of the [1,5] hydrogen shift. We shall discuss this case in some detail since it leads to interesting conclusions and has pedagogical value. Now, a [1,5] hydrogen shift will necessarily compete with a [1,3] hydrogen shift and an operationally useful analysis involves comparing the relative stabilization of the [1,3] and [1,5] suprafacial migration pathways. In both cases, the migration framework is the pentadienyl residue and the migrating group the hydrogen atom.



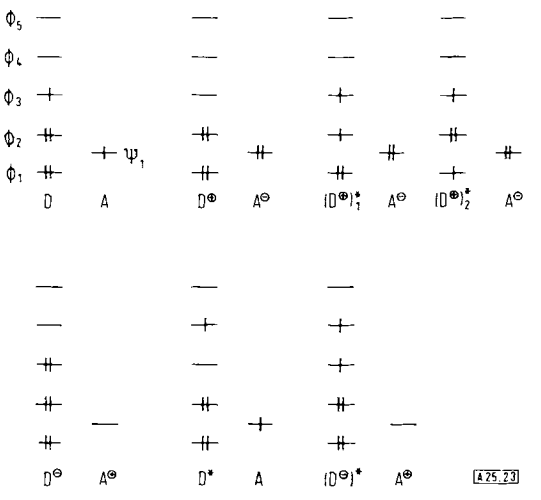


Fig. 23. Basis set configurations for a [1,5] hydrogen sigmatropic shift.

The basis set configurations are shown in Fig. 23. The MOs of the two fragments are:

$$\phi_1 = C_{11}p_1 + C_{12}p_2 + C_{13}p_3 + C_{14}p_4 + C_{15}p_5$$
$$\phi_2 = C_{21}p_1 + C_{22}p_2 - C_{24}p_4 - C_{25}p_5$$
$$\phi_3 = C_{31}p_1 - C_{33}p_3 + C_{35}p_5$$
$$\phi_4 = C_{41}p_1 - C_{42}p_2 + C_{44}p_4 - C_{45}p_5$$
$$\phi_5 = C_{51}p_1 - C_{52}p_2 + C_{53}p_3 - C_{54}p_4 + C_{55}p_5$$
$$\psi_1 = S$$

The general interaction matrix is shown in Scheme 7.

We now wish to explicitly evaluate the MO integrals of the interaction matrix in suprafacial [1,3] and [1,5] hydrogen migration.

Suprafacial [1,3] hydrogen shift

$$\langle\phi_1|H'|\psi_1\rangle = \langle\phi_1|H_{16}|\psi_1\rangle + \langle\phi_1|H_{36}|\psi_1\rangle = C_{11}\gamma_{16} + C_{13}\gamma_{36}$$
$$\langle\phi_2|H'|\psi_1\rangle = \langle\phi_2|H_{16}|\psi_1\rangle + \langle\phi_2|H_{36}|\psi_1\rangle = C_{21}\gamma_{16} + 0$$
$$\langle\phi_3|H'|\psi_1\rangle = \langle\phi_3|H_{16}|\psi_1\rangle + \langle\phi_3|H_{36}|\psi_1\rangle = C_{31}\gamma_{16} + 0$$
$$\langle\phi_4|H'|\psi_1\rangle = \langle\phi_4|H_{16}|\psi_1\rangle + \langle\phi_4|H_{36}|\psi_1\rangle = C_{41}\gamma_{16} + 0$$

Suprafacial [1,5] hydrogen shift

$$\langle\phi_1|H'|\psi_1\rangle = \langle\phi_1|H_{16}|\psi_1\rangle + \langle\phi_1|H_{56}|\psi_1\rangle = C_{11}\gamma_{16} + C_{15}\gamma_{56}$$
$$\langle\phi_2|H'|\psi_1\rangle = \langle\phi_2|H_{16}|\psi_1\rangle + \langle\phi_2|H_{56}|\psi_1\rangle = 0$$
$$\langle\phi_3|H'|\psi_1\rangle = \langle\phi_3|H_{16}|\psi_1\rangle + \langle\phi_3|H_{56}|\psi_1\rangle = C_{31}\gamma_{16} + C_{35}\gamma_{56}$$
$$\langle\phi_4|H'|\psi_1\rangle = \langle\phi_4|H_{16}|\psi_1\rangle + \langle\phi_4|H_{56}|\psi_1\rangle = 0$$

	DA	$D^{\oplus}A^{\ominus}$	$(D^{\oplus})^{\dagger}A^{\ominus}$	$(D^{\oplus})^{\ddagger}A^{\ominus}$	$D^{\ominus}A^{\oplus}$	D*A	$(D^{\ominus})^{*}A^{\oplus}$
DA	X						
$D^{\oplus}A^{\ominus}$	$\langle\phi_3\|H'\|\psi_1\rangle$	X					
$(D^{\oplus})^{\dagger}A^{\ominus}$	$\langle\phi_2\|H'\|\psi_1\rangle$	0	X				
$(D^{\oplus})^{\ddagger}A^{\ominus}$	$\langle\phi_1\|H'\|\psi_1\rangle$	0	0	X			
$D^{\ominus}A^{\oplus}$	$\langle\phi_3\|H'\|\psi_1\rangle$	0	0	0	X		
D*A	0	$\langle\phi_4\|H'\|\psi_1\rangle$	0	0	0	X	
$(D^{\ominus})^{*}A^{\oplus}$	$\langle\phi_4\|H'\|\psi_1\rangle$	0	0	0	0	$\langle\phi_3\|H'\|\psi_1\rangle$	X

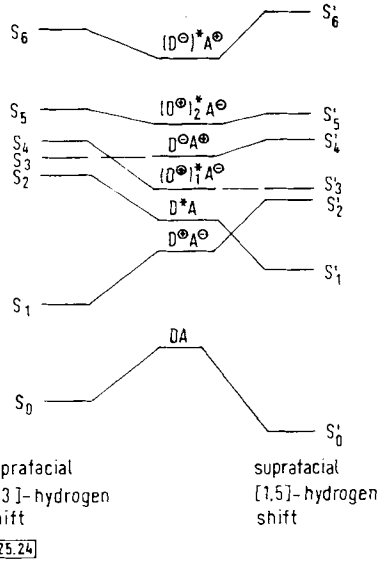
Scheme 7. General interaction matrix for a [1,5] hydrogen shift.

It is quite apparent that we have three kinds of matrix elements of the form $\langle\phi|H_A|\psi\rangle+\langle\phi|H_B|\psi\rangle$:

a) A matrix element where both MO integrals are finite. This leads to mixing of the respective configurations and to pericyclic bonding.

b) A matrix element where the two MO integrals have equal magnitudes but opposite signs. This leads to zero mixing of the respective configurations.

c) A matrix element where one MO integral is finite but the other is zero. This leads to mixing of the respective configurations but *not to pericyclic bonding*. In other words, there is bonding between H and only one of the two migration centers.



A 25.24

Fig. 24. Configuration interaction diagram for competitive suprafacial [1,3] and [1,5] hydrogen sigmatropic shifts.

The configuration interaction diagram for competing [1,5] and [1,3] hydrogen shifts is shown in Fig. 24. The most interesting revelation is that only two of the seven states for [1,3] migration (S_0 and S_5) involve pericyclic bonding. On the other hand, six of the seven states for [1,5] migration involve pericyclic bonding, and only one (S'_3) is a non bonding state. An examination of the configuration interaction diagram leads to the following conclusions:

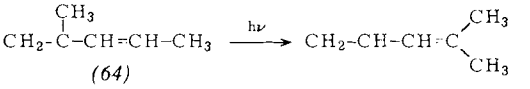
a) A thermal concerted [1,5] shift will dominate over a competitive [1,3] shift.

b) A photochemical *concerted* [1,5] shift will also dominate over a competitive concerted [1,3] shift because S'_1 has lower energy than S_5.

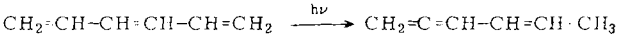
The first conclusion is an expected one and evidence in its support is plenty[104]. However, the second conclusion is novel and the direct consequence of nodal surfaces through C_3 in ϕ_2, ϕ_3, ϕ_4 of the pentadienyl radical, the migration framework for the two competitive sigmatropic shifts.

The previous discussion was concerned only with suprafacial hydrogen shifts. Now, an antarafacial [1,5] hydrogen shift can be a viable alternative[105]. By going through the same analysis as before, we can show that such a shift will be stabilized less than the suprafacial one in thermal cases. An antarafacial [1,5] hydrogen shift, on the other hand, can proceed *via* an excited pericyclic state, which has lower energy than the excited states responsible for photochemical suprafacial [1,3] and [1,5] hydrogen migration. To put it crudely, a [1,5] shift will dominate over a competitive [1,3] shift in both thermal and photochemical reactions.

Thermal preference for [1,5] over [1,3] hydrogen shifts has been amply demonstrated. The novel conclusion that a photochemical [1,5] hydrogen shift (suprafacial or antarafacial) will dominate over a competitive suprafacial [1,3] sigmatropic shift is supported experimentally, *e.g.* by the reactions of *(64)* and *(65)*[106]. Other examples are known[107].



(64)



(65)

A note of caution: When a photochemical [1,5] sigmatropic shift is impossible because of the geometric constraints of the system, a photochemical [1,3] sigmatropic shift of hydrogen can be observed. The latter may be a concerted reaction proceeding *via* S_5. Such examples have been reported in the literature[108].

8. The Nature of Thermal and Photochemical Pericyclic Reactions

Our configuration interaction treatment can serve as the basis for understanding not only the stereoselectivity of thermal pericyclic reactions, but also for understanding the effect of substituents on the rates of such reactions, which proceed either *via* a least motion path or a nonleast motion path[109]. Table 1 illustrates the relative stabilization of typical pericyclic reactions at the nonpolar and polar ends of the reactivity spectrum. Examination of Table 1 leads to formulation of the following general rule: the rate of a concerted pericyclic reaction will increase, irrespective of its stereochemistry, as the polarity of the reaction increases. Or to put it simply, the more polar a reaction is the faster it will be. Experimental data which illustrate this generalization are given below.

1. Cycloadditions. It is well known that the rates of [2+2] cycloadditions increase as the polarity of the reaction increases. Furthermore, the effect of substituents on the rates of the Diels-Alder reactions (Table 2) is well known and in accord with our predictions.

Table 1. Electronic stabilization of the transition states of polar and nonpolar pericyclic reactions.

Pericyclic Reaction	Nonpolar	Polar
1. Cycloadditions		
[2s + 2s]	Zero	Intermediate
[2s + 2a]	Small	Large
[4s + 2s]	Small	Large
[4s + 2a]	Zero	Intermediate
2. Ring Closures		
4*n* Conrotatory	Small	Large
4*n* Disrotatory	Zero	Intermediate
4*n* + 2 Conrotatory	Zero	Intermediate
4*n* + 2 Disrotatory	Small	Large
3. Sigmatropic Shifts		
[1,3] Suprafacial-Inversion	Intermediate	Large
[1,3] Suprafacial-Retention	[a]	[a]
[1,5] Suprafacial-Inversion	[a]	[a]
[1,5] Suprafacial-Retention	Intermediate	Large

[a] The difference between the electronic stabilization of the polar and the nonpolar reactions is small.

Table 2. Reaction of dienophiles with cyclopentadiene and 9,10-dimethylanthracene in dioxane.

Dienophile	Cyclopentadiene $10^5 k_2$ at 20 °C [l mol^{-1} s^{-1}]	9,10-Dimethylanthracene $10^6 k_2$ at 20 °C [l mol^{-1} s^{-1}]
Tetracyanoethylene	≈43000000	≈13000000000
Tricyanoethylene	483000	5880000
1,1-Dicyanoethylene	45500	127000
Fumaronitrile	81	139
Maleonitrile	91	131
Acrylonitrile	1.04	0.89

2. Electrocyclic reactions. The relative rates of the ring opening of *(66)* and *(67)* are given under the formulas. Increased electron acceptor ability of one of the two fragments in *(67)* is accompanied by enhanced reaction rates[110].

(66) 

$k_{rel}(25\,°C) = 1$

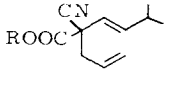
 *(67)*

$k_{rel}(25\,°C) = 10^7$

3. Sigmatropic shifts. The rate of a Cope rearrangement increases as the two reaction fragments—formal allyl radicals—aquire opposite polarity[111]. Examples are compounds *(68)*—*(71)*.

(68) 

E_a = 35.3 kcal/mol

 *(69)*

E_a = 28.6 kcal/mol

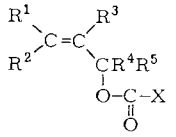
(70) 

E_a = 34.2 kcal/mol

 *(71)*

E_a = 27.9 kcal/mol

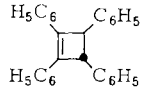
Furthermore, the rates of sigmatropic rearrangements of molecules such as *(72)* increase as the substituents R^1—R^5 become more electron releasing and the X substituent becomes more electronegative[112].

 *(72)*

It should be emphasized that our approach can be readily extended to cases where both reaction fragments act as good electron acceptors and electron donors simultaneously. This occurs when the two fragments are highly conjugated systems having a high lying HOMO and a low lying LUMO. As a result, increasing the conjugation of the two reaction fragments is expected to lead to increasing reaction rates. This is nicely illustrated by the cycloreversions of the cyclobutenes *(73)* and *(74)*[113].

(73) 

E_a = 32.5 kcal/mol

 *(74)*

E_a = 21.0 kcal/mol

At this point, it should be mentioned that ring opening of cyclobutenes might involve two separate phases: a phase involving rotation followed by a phase involving bond formation[19]. Hence substituents can affect the energetics of both phases of the mechanism; our approach is pertinent to the rotation part of the aforementioned mechanism only.

We hope that this discussion of the rates of pericyclic reactions will put to rest such obscure ideas as "substituent effects on concerted reactions are expected to be small" or "the rate of a concerted reaction borrows from the rate of the corresponding nonconcerted process", *etc.*

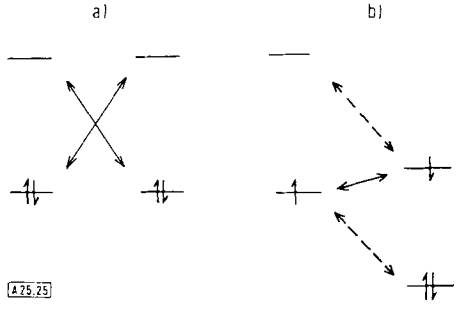


Fig. 25. Configuration interaction diagram for a) nonpolar [2+2] cyclodimerization and b) polar [2+2] cycloaddition. Solid arrows indicate the dominant MO interactions stabilizing [2s+2a] union and broken line arrows indicate those which stabilize [2s+2s] union. Only the HOMOs and LUMOs of the cycloaddends are shown.

A correct and general theoretical treatment of any organic chemistry problem should lend itself to simplification. Figure 25 illustrates how our detailed configuration interaction analysis of thermal [2+2] cycloaddition can be briefly summarized by means of interaction diagrams. This simple approach was initially described by us[10], and constitutes an easy way

for visualizing how reversal of the Woodward-Hoffmann rules can occur in thermal reactions. In the case of nonpolar cycloadditions, the major contributor to the resonance hybrid of the transition complex is the no bond configuration DA. On the other hand, in the case of polar cycloadditions, the charge transfer configuration $D^{\oplus}A^{\ominus}$ is the major contributor. Accordingly, the stereoselectivity of nonpolar cycloadditions will depend on the orbital interactions which obtain in DA, while the stereoselectivity of polar cycloadditions will depend on the orbital interactions which obtain in $D^{\oplus}A^{\ominus}$. In nonpolar [2+2] cycloadditions orbital interactions in DA can only stabilize the [2s+2a] transition state complex, whereas in polar [2+2] cycloadditions orbital interactions can stabilize both [2s+2a] and [2s+2s] transition state complexes. We can analyze in a similar manner the stereoselectivity of semipolar and polar [4+2] cycloadditions.

The nature of the transition state complex in Woodward-Hoffmann allowed and forbidden pericyclic reactions is different, as revealed by our configuration interaction approach. In short, reversal of the Woodward-Hoffmann rules in polar thermal reactions can be traced to the existence of a low energy charge transfer configuration $D^{\oplus}A^{\ominus}$ as well as to the existence of an appropriate excited state which can mix with $D^{\oplus}A^{\ominus}$ and give rise to pericyclic bonding.

The rates of pericyclic photochemical reactions cannot be discussed in any reliable qualitative manner, unless more is known theoretically and experimentally about the process of internal energy conversion[114]. However, our configuration interaction analysis can provide interesting insights into the nature of the transition state complexes involved in photochemical reactions. According to such analysis there are two types of pericyclic photochemical reactions described by the following equations:

$$D + A^* \longrightarrow [\text{excimer complex}]^* \begin{array}{l} \xrightarrow{a} P \\ \xrightarrow{b} P^* \longrightarrow P \end{array} \qquad (7)$$

$$D + A^* \longrightarrow [\text{charge-transfer complex}]^* \begin{array}{l} \xrightarrow{a} P \\ \xrightarrow{b} P^* \longrightarrow P \end{array} \qquad (8)$$

The Woodward-Hoffmann allowed reactions proceed according to the first mechanism. In the case of polar photochemical reactions, the Woodward-Hoffmann rules are reversed because there is an excited charge transfer state which has lower energy than the corresponding excimer state.

At this point, we wish to digress, and point out that the two mechanistic schemes proposed on the basis of our analysis have been justified, in an entirely different context, by spectroscopic studies. The first mechanism [cf. eq. (7)] involves the transformation of D and A* (or D* and A) to an excimer complex which is primarily made up of the charge transfer configurations $D^{\oplus}A^{\ominus}$ and $D^{\ominus}A^{\oplus}$ as well as the locally excited configurations D*A and DA*. Hence, this transformation is an allowed one. Decay of the excimer to P* (P=product) is most likely because the excimer contains the locally excited configurations D*A and DA*. On the other hand, decay of the excimer to P is also possible because the excimer contains a small amount of the no bond configuration DA as a result of vibrationally induced mixing. This vibrationally induced mixing, which is bound to be significant in the transition state, is nothing else but a form of asymmetry induced mixing which we have previously discussed. Hence, both paths a and b can be followed. The second mechanism [eq. (8)] involves the transformation of D and A* (or D* and A) to an excited charge transfer complex which is primarily made up of the charge transfer configurations $D^{\oplus}A^{\ominus}$ and $D^{\ominus}A^{\oplus}$ as well as the no bond configuration DA. Now, vibrationally induced mixing, which is expected to be significant in the transition state, can endow the excited charge transfer with substantial D*A and DA* character and render the transformation allowed. This vibration induced mixing is, once again, nothing else but a form of asymmetry induced mixing which we have previously discussed. Spectroscopic results support this argument[115]. Laser experiments have shown that the following excitations are possible:

$$(D^{\ominus}A^{\ominus})^* \xrightarrow{h\nu} (A^*D)$$

$$(D^{\oplus}A^{\ominus})^* \xrightarrow{h\nu} (AD^*)$$

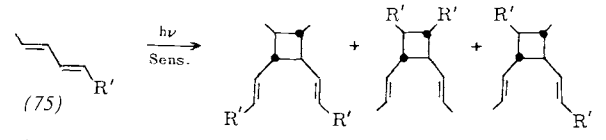
These are "reverse charge transfer transitions", which are allowed because of the presence of locally excited configurations in $(D^{\oplus}A^{\ominus})^*$. This allowedness is bound to be even more marked in photochemical reactions. Decay of the excited charge transfer complex to P is most likely because the former contains principally the no bond configuration DA. Once again, both paths a and b can be followed.

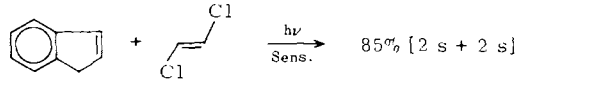
Finally, a satisfying reactivity pattern remains to be pointed out. Photochemical reactions proceeding *via* excimeric states will be electronically predisposed to have opposite stereoselectivity to those proceeding thermally because in the former case stereoselectivity is mainly determined by the mixing of $D^{\oplus}A^{\ominus}$, $D^{\ominus}A^{\ominus}$, D*A and DA* while in the latter it is determined by the mixing of $D^{\oplus}A^{\ominus}$, $D^{\ominus}A^{\oplus}$ and DA. In contrast, photochemical reactions proceeding *via* charge transfer states will be electronically predisposed to have the same stereoselectivity as those proceeding thermally because in both cases stereoselectivity is mainly determined by the mixing of $D^{\oplus}A^{\ominus}$, $D^{\ominus}A^{\oplus}$ and DA.

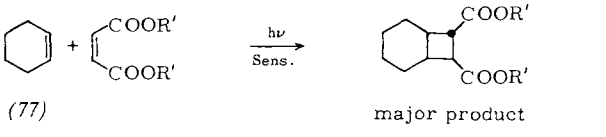
Our detailed configuration interaction analysis of photochemical cycloadditions can be conveniently summarized by means of MO interaction diagrams. The transition state complex of the photoreaction can be assumed to be a resonance hybrid of the D*A (or, DA*) and $D^{\oplus}A^{\ominus}$ contributors. The stereoselectivity of nonpolar cycloadditions will depend on the orbital interactions which obtain in D*A and that of polar cycloadditions on the orbital interactions in $D^{\oplus}A^{\ominus}$. In most cases, one is led to similar conclusions by simply examining the dominant interactions of energy-close orbitals in D*A in both nonpolar and polar cycloadditions. These simple approaches, leading to the same conclusions as the present more detailed approach, have been discussed in a series of papers[110].

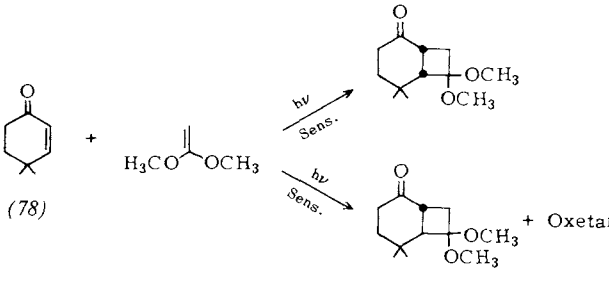
Our analysis of photochemical reactions is formally applicable to singlet reactions. However, one can envision situations where spin orbit coupling could render triplet reactions effectively equivalent to singlet reactions. Spin orbit coupling is facilitated by charge transfer complexation of the triplet excited molecule[116] and, as we have seen, all transition states of photochemical pericyclic reactions have charge transfer contributions which vary from strong (excimer type transition states) to extremely strong (charge transfer type transition states).

Accordingly, *the fact that a singlet and a triplet reaction have the same stereoselectivity does not necessarily mean that both reactions occur via a common intermediate.* It may very well mean that both reactions are concerted and spin orbit coupling is strong. On the other hand, if a singlet and a triplet reaction exhibit different stereoselectivity and product distribution, this can be taken to be a strong indication of mechanistic duality. A survey of the experimental results reported on sensitized photocycloadditions reveals that many triplet photocycloadditions occur with a stereoselectivity which is expected for concerted singlet photocycloadditions[117]. In our opinion, this could indicate that spin orbit coupling can give rise to rapid spin flipping and the triplet photocycloadditions can thus exhibit the stereoselectivity expected from singlet concerted photocycloadditions. Examples are the nonpolar sensitized [2s+2s] photocycloadditions of compounds *(75)* and *(76)*[118,119] and the polar sensitized [2s+2a] photocycloadditions of compounds *(77)* and *(78)*[120].

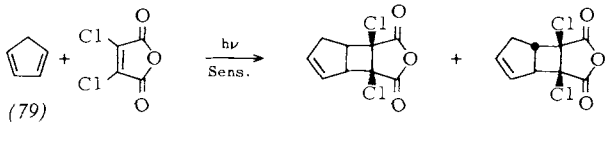








In the reaction of *(78)*, the two stereoisomeric states arise from two different triplet states: a triplet reaction can be stereospecific! The amazing stereoisomerism exhibited by the products of the polar, sensitized photocycloaddition of *(79)* is a strong indication that a [2s+2a] reaction is competing with a [2s+2s] reaction, despite the unfavorable steric features of the former type of union[121].

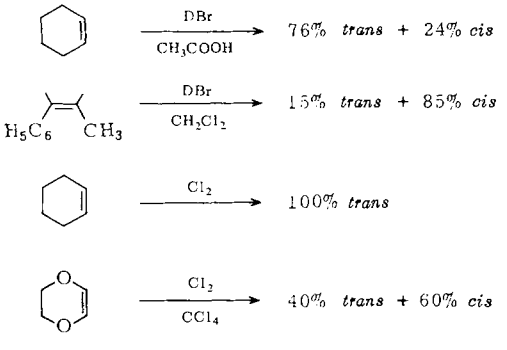


It should be pointed out that in some of the above reactions, the presence of a heavy atom substituent can additionally enhance spin orbit coupling. Here, we should like to bring the reader's attention to an interesting paper by *Ross* and *George*[8] in which the formal inapplicability of the Wigner-Wittmer spin rules to chemical reactions are discussed.

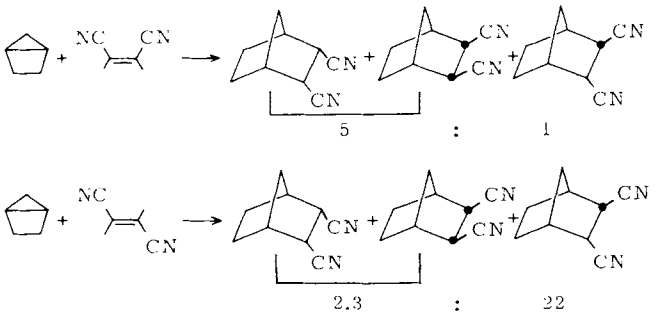
A final point remains to be made: We have derived stereoselection rules for photochemical reactions under the assumption that these reactions occur *via* the lowest excited state of the "transition state complex". We can designate this entity as the photoreaction complex. Our approach predicts that there are two types of photoreaction complexes, one resembling an excited charge transfer complex and another resembling an excimer. In each reaction, these two types of complexes lead to different stereoselectivities. This simple picture seems to be reasonable for reactions where the reactants and the photoreaction complex have similar degrees of conjugation, as is the case in photocycloadditions and photochemical cyclizations. On the other hand, when the reactants are less conjugated than the photoreaction complex, as in the case of photochemical cycloreversions, ring openings, sigmatropic rearrangements, *etc.*, it is possible that a different situation may exist. The photoexcitation of the reactant may involve sufficient energy so that a higher excited state of the photoreaction complex is reached. This higher state can either decay directly to the ground state product or yield an excited product which can subsequently decay to its ground state[122]. Our configuration interaction analysis describes the multitude of higher excited states of the photoreaction complex for each stereochemical mode. Hence, there is a hope that the stereoselectivities of photochemical reactions which proceed *via* a higher excited state can be eventually unterstood in terms of our approach.

In this work, we have examined the stereoselectivity and rates of concerted cycloadditions and cycloreversions, electrocyclic reactions and sigmatropic rearrangements[123]. Naturally, the same concepts can be applied to other general types of reactions, such as electrophilic additions to double bonds, additions of strained bicyclics to olefins, additions of benzynes to olefins, exchange reactions, ionic rearrangements, *etc.* In these cases, the experimental evidence seems to support strongly our qualitative conclusions. For example, the following trends are observed:

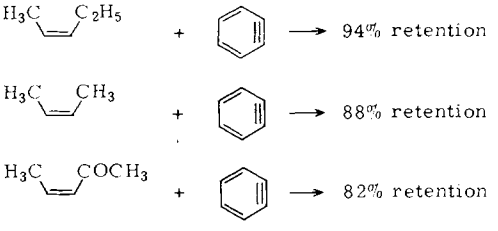
1. In the case of electrophilic additions to double bonds, increasing the electron donating ability of the olefin leads to increased *cis* stereoselectivity[124–127].



2. Strained bicyclic molecules can add to electron acceptor olefins with a high degree of *cis* stereoselectivity[128].



3. Benzyne adds to electron rich *cis* olefins with a high degree of *cis* stereoselectivity[129].

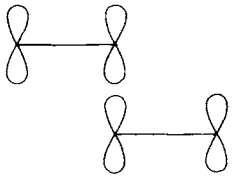


9. The Question of the Intermediate

We now wish to take a closer look at the concept of diradical and dipolar intermediates[130]. Such intermediates can be operationally definable in cycloaddition reactions. Hence, we shall restrict our attention to such reactions and, in particular, discuss the case of [2+2] cycloaddition. Many workers seem to neglect the important fact that diradical or dipolar intermediates must be formed in a transoid geometry so that the two ends do not overlap. Assymmetric overlap of all uniting centers would lead to a variant of a concerted reaction. For example, consider the case of a [2+2] cycloaddition proceeding *via* a stepwise mechanism:



The rate determining step of the reaction can be step 1 or step 2. In the former case, our configuration interaction analysis can lead to an insight as to whether a stepwise or a concerted mechanism will be operative in [2+2] cycloaddition. The electronic states of the transition complexes of [2s+2s] and [2s+2a] concerted reactions, as well as the electronic states for the diradicaloid[131] transition state *(80)*, can be derived in the same manner as before, so that their relative energies can be compared.



(80)

Maximum configuration mixing can take place in the case of this diradicaloid transition state, but the matrix elements will be roughly half the size compared to the nonzero matrix elements of the [2s+2s] and [2s+2a] transition states. Construction of the appropriate configuration interaction diagrams and consideration of the steric features of the various transition states leads to the following conclusions:

a) In nonpolar [2+2] cycloadditions, the transition states of the thermal [2s+2a] and the photochemical [2s+2s] reactions are electronically stabilized. The transition state of the stepwise reaction is also stabilized, though less so than the transition states of the concerted reactions. However, steric effects can destabilize the thermal [2s+2a] pathway but not the photochemical [2s+2s] pathway. As a result, a stepwise mechanism involving diradical intermediates can dominate over the thermal [2s+2a] mechanism but cannot dominate over the photochemical [2s+2s] mechanism, unless the photoexcited cycloaddend reacts in a nearly perpendicular geometry.

b) In polar [2+2] cycloadditions, the thermal [2s+2a] reaction is stabilized to a greater extent electronically than either the [2s+2s] or the stepwise reaction. The latter two are stabilized electronically to comparable extents. The unfavorable steric features of the [2s+2a] transition state render the [2s+2s] and stepwise pathways more favorable, so that polar thermal [2+2] cycloadditions are expected to occur *via* competitive converted ([2s+2s]) and stepwise mechanisms. The photochemical reaction, however, is predicted to proceed preferably *via* an excited intermediate and this pathway is expected to dominate over the concerted ([2s+2a]) reaction. According to these conclusions, one expects that polar thermal [2+2] cycloadditions and, even more so, polar [2+2] photocycloadditions will be nonstereoselective because they involve a transoid intermediate which can exhibit free bond rotation before ring closure. As we have already seen, the experimental results are in disagreement with such inferences.

The above considerations are valid only if the transition state for a stepwise reaction occurs between the reactants and the transoid intermediate. This hypothesis is of dubious validity in the case of nonpolar reactions and is probably incorrect in the case of polar reactions. Conversion of the transoid intermediate into the product requires some activation energy for rotation about the C^2—C^3 bond to yield the cisoid intermediate, and further activation energy for ring closure of the latter to product. Now, ring closures of diradical intermediates could be associated with substantial barriers, which, according to thermochemical calculations by *Benson* and *O'Neal*[132], amount to approximately 6 kcal/mol. Furthermore, barriers to rotation about the C^2—C^3 bond can be substantial when C^1 and C^4 bear substituent groups. If we assume that the activation energy for the decomposition of a diradical back to reactants is of the order of magnitude of 6 kcal/mol, the approximate activation energy for the decomposition of the tetramethylene diradical, we are led to the conclusion that the transition state for nonpolar [2+2] cycloadditions most likely lies between the intermediate transoid diradical and the products. In polar [2+2] cycloadditions, there is an additional factor which has to be considered—the solvation energy of the two ends of the dipolar intermediate which is lost as a result of ring formation and which can be very large[133]. Hence, in polar [2+2] cycloadditions the transition state of the stepwise process is fully expected to lie between the transoid dipolar intermediate and the product.

The following conclusion is reached: in polar cycloadditions, and possibly in nonpolar cycloadditions, one cannot use a

transoid diradicaloid transition state model in order to draw quantum mechanical inferences about the stereochemistry, rate, *etc.* of such reactions[1,3,4]. If the energy of a transoid diradicaloid transition state is calculated by a quantum mechanical method, then one has to add the energy difference between the transition state for step 1 and the transition state for step 2 in order to assess correctly the energy of the transition state of the stepwise reaction.

We can now return to our configuration interaction analysis of the electronic states of diradicaloid transition states. If step 2, and not step 1 as we previously assumed, is rate determining, one has to correct the energies of the transoid diradicaloid states to higher energies. Thus, in nonpolar thermal cycloadditions the stepwise mechanism and the concerted [2s+2a] mechanism will become competitive, while in nonpolar photochemical cycloadditions the [2s+2s] mechanism will dominate over the stepwise mechanism, unless the photoexcited cycloaddend reacts from a nearly perpendicular geometry. Furthermore, in polar thermal cycloadditions the [2s+2s] mechanism will dominate over the stepwise mechanism, while in polar photochemical cycloadditions the [2s+2a] mechanism will compete with, and may even dominate over, the stepwise mechanism.

In short, we believe that there are qualitative reasons for expecting concerted reactions to dominate over their stepwise alternatives, with the exception of nonpolar thermal [2+2] and, possibly, semipolar thermal [4+2] cycloadditions. In addition, experimental results show that the expected stereorandomness of reactions proceeding *via* diradical or dipolar intermediates does not obtain in most cases. Hence, predominantly, although not necessarily exclusively, concerted reactions seem to be good candidates for a plausible interpretation of the origin of stereoselectivity.

10. Conclusion

In this work, we described a simple configuration interaction approach for the treatment of pericyclic reactions. We utilized a Hamiltonian which contained only one-electron parts and, hence, allowed the mixing only of configuration wave functions which differed at most by one spin orbital. Inclusion of two-electron parts in our Hamiltonian will allow mixing of configuration wave functions which differ at most by two spin orbitals. Ultimately, inclusion of one-electron and two-electron terms along with an expanded configuration basis set can produce a computational scheme of sufficient quantitative accuracy. The effect of two-electron mixing on the stereoselectivity of thermal pericyclic reactions has been discussed by us in a series of papers and has been shown to parallel quite closely the effect of one-electron mixing. Accordingly, we believe that the dichotomy between nonpolar and polar pericyclic reactions is a real one and further experimental studies will most likely bear this point out. We now would like to make some remarks pertaining to the Woodward-Hoffmann rules:

a) In the case of thermal reactions the electronically preferred stereochemical mode of union of two cycloaddends or fragments is predicted to be the same by both the Woodward-Hoffmann rules and the configuration interaction treatment. However, the configuration interaction treatment reveals that in polar reactions, an alternative stereochemical mode of union can also be electronically stabilized.

b) In the case of thermal reactions, the Woodward-Hoffmann orbital symmetry approach can provide the framework for discussing two-electron configuration interaction effects. As we have discussed before, diexcitation is energetically inexpensive in polar reactions and can lead to congruence of the orbital symmetry characteristics of the transition state complex and the products in Woodward-Hoffmann forbidden reactions.

c) In polar photochemical cycloadditions, the configuration interaction treatment leads to stereochemical predictions which are opposite to the ones of Woodward and Hoffmann because the importance of charge transfer excitation is paramount. However, even in this instance the orbital symmetry approach rises to the occasion. Thus, the opposite stereoselectivities of a nonpolar and a polar photochemical [4+2] cycloaddition can be predicted by using orbital symmetry arguments. Figure 26 shows the orbital symmetry correlation diagrams for a nonpolar and a polar suprafacial [4+2] photocycloaddition. In the semipolar case there is no congruence between the orbital symmetry characteristics of the lowest excited state of the reactants (a locally excited state) and either the lowest excited state or the ground state of the product. By contrast, in polar [4+2] photocycloadditions, the lowest excited state of the reactants (a charge transfer state) correlates with a higher excited state of the product or *directly with the ground state of the product*. Here, we have a case where orbital symmetry can dictate the mechanism of the reaction, as well as its stereoselectivity. Polar [4+2] cycloadditions are [4s+2s] stereoselective and proceed by the following mechanism:

$$D^* + A \rightarrow (D^{\delta+} \cdots A^{\delta-})^*_{CT} \rightarrow DA$$

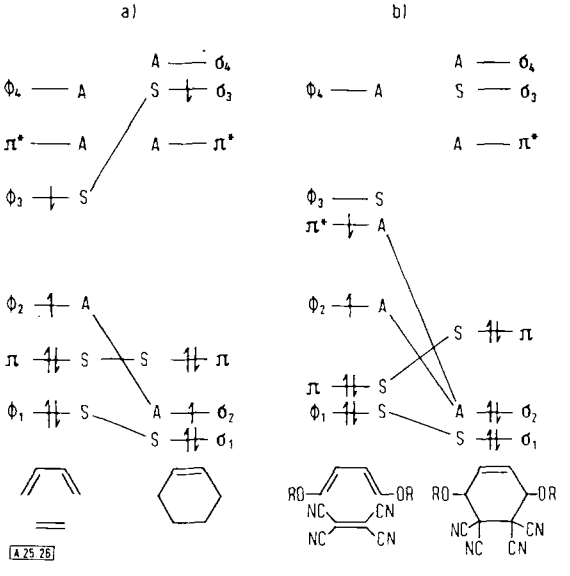


Fig. 26. Correlation diagram for a) a semipolar and b) a polar, suprafacial [4+2] cycloaddition. ϕ_1, ϕ_2, ϕ_3, and ϕ_4 are the π MOs of the unperturbed or perturbed butadiene and π and π^* are the π MOs of the unperturbed or perturbed ethylene. The MO correlations are to be considered as "intended" correlations.

In short, the principle of conservation of orbital symmetry provides a convenient theoretical framework for exploring the stereoselectivity of both nonpolar and polar pericyclic reactions, if one wishes to do so. However, the configuration

interaction approach is simple enough, able to reveal reactivity trends, and can be used to analyze problems where symmetry is totally absent.

The fundamental ideas and the theoretical approach reported in this work have been stimulated by past important contributions of able theorists. The work of *Mulliken* on molecular complexes[135] provided the initial stimulus for this work. The configuration interaction approach discussed in this paper was put forward by *Mulliken* and also by *Longuet-Higgins* and *Murrell*[136] in their studies of the electronic states of unsaturated molecules[137]. Finally, it would have been an unforgivable oversight not to emphasize that the concepts outlined here are the indirect result of countless experimental contributions of able investigators.

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[1] For a full account of the classic work of *Woodward* and *Hoffmann*, see: *R. B. Woodward* and *R. Hoffmann*: The Conservation of Orbital Symmetry. Academic Press, New York 1970 and Verlag Chemie, Weinheim 1970; Angew. Chem. *81*, 797 (1969); Angew. Chem. internat. Edit. *8*, 781 (1969). See also: *H. C. Longuet-Higgins* and *E. W. Abrahamson*, J. Amer. Chem. Soc. *87*, 2045 (1965).

[2] *M. J. S. Dewar*, Angew. Chem. *83*, 859 (1971); Angew. Chem. internat. Edit. *10*, 761 (1971).

[3] *H. E. Zimmerman*, Accounts Chem. Res. *4*, 272 (1971).

[4] *K. Fukui*, Accounts Chem. Res. *4*, 57 (1971).

[5] *L. Salem*, J. Amer. Chem. Soc. *90*, 543, 553 (1968).

[6] *C. Trindle*, J. Amer. Chem. Soc. *92*, 3251, 3255 (1969).

[7] *W. A. Goddard III*, J. Amer. Chem. Soc. *94*, 793 (1972).

[8] *T. F. George* and *J. Ross*, J. Chem. Phys. *55*, 3851 (1971).

[9] *J. Langlet* and *J.-P. Malrieu*, J. Amer. Chem. Soc. *94*, 7254 (1972); *W. T. van der Hart*, *T. T. C. Mulder*, and *L. J. Oosterhoof*, J. Amer. Chem. Soc. *94*, 5724 (1972).

[10] *N. D. Epiotis*, J. Amer. Chem. Soc. *94*, 1924, 1935, 1941, 1946 (1972).

[11] *N. D. Epiotis*, J. Amer. Chem. Soc. *95*, 1191, 1200, 1206, 1214 (1973).

[12] *C. Sandorfy*: Electronic Spectra and Quantum Chemistry, Prentice-Hall, Englewood Cliffs, N. J., 1964.

[13] *R. F. W. Bader*, Can. J. Chem. *40*, 1164 (1962).

[14] *L. Salem* and *J. S. Wright*, J. Amer. Chem. Soc. *91*, 5947 (1969).

[15] *R. G. Pearson*, Accounts Chem. Res. *4*, 152 (1971).

[16] *J. E. Baldwin* and *A. H. Andrist*, J. Amer. Chem. Soc. *93*, 3289 (1971); *J. E. Baldwin*, *A. H. Andrist*, and *R. K. Prinschmidt*, *Jr.*, Accounts Chem. Res. *5*, 402 (1973).

[17] *J. Kolc* and *J. Michl*, J. Amer. Chem. Soc. *92*, 4147 (1970).

[18] *W. Schmidt*, Helv. Chim. Acta *54*, 862 (1971); *K. A. Muszkat* and *W. Schmidt*, *ibid. 54*, 1195 (1971); *W. Schmidt*, Tetrahedron Lett. *1972*, 581.

[19] *K. Hsu*, *R. J. Buenker*, and *S. D. Peyerimhoff*, J. Amer. Chem. Soc. *93*, 2117 (1971); *R. J. Buenker*, *S. D. Peyerimhoff*, and *K. Hsu*, *ibid. 93*, 5005 (1971).

[20] *R. C. Bingham* and *M. J. S. Dewar*, J. Amer. Chem. Soc. *96*, 9107 (1972).

[21] *F. S. Collins*, *J. K. George*, and *C. Trindle*, J. Amer. Chem. Soc. *94*, 3732 (1972).

[22] a) *R. A. Jackson*, J. Chem. Soc. *B 1970*, 58; b) *L. M. Raff* and *R. N. Porter*, J. Chem. Phys. *51*, 4701 (1969).

[23] *J. A. Berson* and *L. Salem*, J. Amer. Chem. Soc. *94*, 8917 (1972).

[24] *S. P. McGlynn*, *A. T. Armstrong*, and *T. Azumi*, Mod. Quantum Chem. Lect. Istanbul Int. Summer Sch. *3* (1965).

[25] *A. S. Davidov*: Theory of Molecular Excitons. McGraw-Hill, New York 1962.

[26] Such calculations are described in articles on charge transfer interactions. See: *R. S. Mulliken*, J. Amer. Chem. Soc. *74*, 811 (1952); *L. J. Andrews* and *R. M. Keefer*: Molecular Complexes in Organic Chemistry. Holden-Day, San Francisco 1964.

[27] *M. J. S. Dewar*: The Molecular Orbital Theory of Organic Chemistry. McGraw-Hill, New York 1969; *R. Hoffmann*, Accounts Chem. Res. *4*, 1 (1971).

[28] For example, the regioselectivity of a reaction can be determined by such a method.

[29] These simple rules are to be found in most textbooks on quantum chemistry. See *e.g.*: *L. Salem*: The Molecular Orbital Theory of Conjugated Systems. Benjamin, New York 1966.

[30] Proportionality constants which precede the MO integrals are omitted for conservation of space.

[31] The magnitudes of the coulombic terms C and C in the energy expressions for $D^{\oplus}A^{\ominus}$ and $D^{\ominus}A^{\oplus}$ depend on the geometry of approach of the two cycloaddends. Hence, the energies of $D^{\oplus}A^{\ominus}$ and $D^{\ominus}A^{\oplus}$ will be slightly different for [s+s] and [s+a] union. In order to simplify the construction of the configuration interaction diagrams for cycloadditions, we have assumed that the energies of $D^{\oplus}A^{\ominus}$ and $D^{\ominus}A^{\oplus}$ configurations are the same for both [s+s] and [s+a] union.

[32] For a review of excimers as distinct photochemical intermediates, see: *T. Förster*, Angew. Chem. *81*, 364 (1969); Angew. Chem. internat. Edit. *8*, 333 (1969).

[33] In this work, the term "excited charge transfer complex" is equivalent to the terms "excited charge transfer complex and exciplex".

[34] *N. D. Epiotis*, unpublished results.

[35] For intermolecular approach distances between 1.75 and 3.0 Å.

[36] *R. Sustmann*, unpublished results, cited in *R. Sustmann* and *H. Trill*, Angew. Chem. *84*, 887 (1972); Angew. Chem. internat. Edit. *11*, 838 (1972).

[37] *A. L. Farragher* and *F. M. Page*, Trans. Faraday Soc. *63*, 2369 (1967).

[38] *E. M. Kosower*, Progr. Phys. Org. Chem. *3*, 81 (1965).

[39] For a related argument see Ref. [4].

[40] On the basis of a one-configuration analysis and PMO calculations, *Herndon* has arrived at similar conclusions: *W. C. Herndon*, Tetrahedron Lett. *1971*, 125; *W. C. Herndon* and *W. B. Giles*, Mol. Photochem. *2*, 277 (1970).

[41] *N. D. Epiotis*, J. Amer. Chem. Soc. *95*, 5624 (1973).

[42] *K. Kraft* and *G. Koltzenburg*, Tetrahedron Lett. *1967*, 4357, 4723.

[43] *A. Padwa*, *W. Koen*, *J. Masaracchia*, *C. L. Osborn*, and *D. J. Trecker*, J. Amer. Chem. Soc. *93*, 3633 (1971).

[44] For examples of intramolecular [2+2] cyclodimerizations and cycloreversions thought to proceed *via* diradical intermediates, see: *L. A. Paquette* and *J. A. Schwartz*, J. Amer. Chem. Soc. *92*, 3215 (1970). However, for a different viewpoint, see: *M. J. Goldstein* and *M. S. Benzon*, *ibid. 94*, 5119 (1972).

[45] *A. T. Cocks*, *H. M. Frey*, and *I. D. R. Stevens*, Chem. Commun. *1969*, 458.

[46] *H. R. Gerberich* and *W. D. Walters*, J. Amer. Chem. Soc. *83*, 3935, 4884 (1961).

[47] *P. D. Bartlett*, *G. M. Cohen*, *S. P. Elliott*, *K. Hummel*, *R. A. Minus*, *C. M. Sharts*, and *J. Y. Fukunaga*, J. Amer. Chem. Soc. *94*, 2899 (1972). The energies of the π HOMO and LUMO of tetrafluoroethylene are similar to those of ethylene. Hence, the electronic stabilization of the [2s+2a] transition state in the cycloaddition of tetrafluoroethylene and ethylene is very much similar to that of the [2s+2a] transition state in the cyclodimerization of two ethylenes.

[48] *J. E. Baldwin* and *P. W. Ford*, J. Amer. Chem. Soc. *91*, 7192 (1969).

[49] *H. E. O'Neal* and *S. W. Benson*, J. Phys. Chem. *72*, 1866 (1968); *H. E. O'Neal* and *S. W. Benson*, Int. J. Chem. Kinet. *1*, 221 (1969).

[50] See also: *E. N. Cain* and *R. K. Solly*, J. Amer. Chem. Soc. *94*, 3830 (1972).

[51] *H. Yamazaki* and *R. J. Cvetanovic*, J. Amer. Chem. Soc. *91*, 520 (1969).

[52] *R. Livingston* and *K. S. Wei*, J. Phys. Chem. *71*, 541 (1967).

[53] *D. O. Cowan* and *R. L. Drisko*, Tetrahedron Lett. *1967*, 1255.

[54] *D. J. Trecker*, Org. Photochem. *2*, 63 (1969).

[55] *J. C. Dalton*, *P. A. Wriede*, and *N. J. Turro*, J. Amer. Chem. Soc. *92*, 1318 (1970).

[56] *S. Proskow*, *H. E. Simmons*, and *T. L. Cairns*, J. Amer. Chem. Soc. *88*, 5254 (1966).

[57] *R. W. Hoffmann*, Angew. Chem. *80*, 823 (1968); Angew. Chem. internat. Edit. *7*, 754 (1968).

[58] *J. Firl* and *S. Sommer*, Tetrahedron Lett. *1972*, 4713.

[59] *P. D. Bartlett* and *A. P. Schapp*, J. Amer. Chem. Soc. *92*, 3223 (1970); *P. D. Bartlett*, Quart. Rev. (London) *24*, 473 (1970). *J. K. Williams*, *D. W. Wiley*, and *B. C. McKusick*, J. Amer. Chem. Soc. *84*, 2210 (1962).

[60] *R. S. H. Liu*, Tetrahedron Lett. *1969*, 1409.

[61] *H. Prinzbach*, *W. Eberbach*, and *G. Philippossian*, Angew. Chem. *80*, 910 (1968); Angew. Chem. internat. Edit. *7*, 887 (1968).

[62] *S. F. Nelsen* and *J. P. Gillespie*, Tetrahedron Lett. *1969*, 3259. For a related example, see: *J. R. Edman*, J. Org. Chem. *32*, 2920 (1967).

[63] *E. T. Corey*, *J. D. Bass*, *R. LeMahieu*, and *R. B. Mitra*, J. Amer. Chem. Soc. *86*, 5570 (1964).

[64] *T. A. Rettig*, Ph. D. Thesis, Iowa-State University, Ames, Iowa 1965.

[65] *R. Robson, P. W. Gruble*, and *J. A. Barltrop*, J. Chem. Soc. *1964*, 2153.

[66] For additional experimental evidence which indicates that the theoretical expectations are met, see: *A. O. Cox, P. de Mayo*, and *R. W. Yip*, J. Amer. Chem. Soc. *88*, 1043 (1966); *R. L. Cargill* and *M. R. Wilcott III*, J. Org. Chem. *31*, 3938 (1966).

[67] *G. Kaupp*, Angew. Chem. *83*, 361 (1971); Angew. Chem. internat. Edit. *10*, 340 (1971). However, in the case of the substituted cyclohexadiene, conformational effects might also be important.

[68] *N. J. Turro* and *P. A. Wriede*, J. Amer. Chem. Soc. *92*, 320 (1970); see also: *D. R. Arnold, R. L. Hinman*, and *A. H. Glick*, cited in Advan. Photochem. *6*, 301 (1968).

[69] A one-configuration MO approach leads to similar conclusions. *W. C. Herndon* and *W. B. Giles*, Chem. Commun. *1969*, 497.

[70] *H. E. O'Neal* and *S. W. Benson*, J. Phys. Chem. *72*, 1866 (1968).

[71] *J. A. Benson* and *A. Remanick*, J. Amer. Chem. Soc. *83*, 4947 (1961).

[72] *I. L. Chow* and *T. C. Joseph*, Chem. Commun. *1968*, 604.

[73] *R. Sustmann*, Tetrahedron Lett. *1971*, 2717, 2721.

[74] *J. Feuer, W. C. Herndon*, and *L. H. Hall*, Tetrahedron *24*, 2575 (1968).

[75] *R. Huisgen, R. Graskey*, and *J. Sauer* in *S. Patai:* The Chemistry of Alkenes. Wiley, New York 1964.

[76] *J. P. Simons*, Trans. Faraday Soc. *56*, 391 (1960).

[77] *N. C. Yang* and *J. Libman*, J. Amer. Chem. Soc. *94*, 1405 (1972); *N. C. Yang, J. Libman, L. Barrett, Jr., M. H. Hui*, and *R. L. Loeschen, ibid. 94*, 1406 (1972).

[78] *J. A. Berson* and *S. S. Olin*, J. Amer. Chem. Soc. *92*, 1086 (1970).

[79] *R. S. Becker* and *E. Chen*, J. Chem. Phys. *45*, 2403 (1966).

[80] *H. F. Angus* and *D. Bryce-Smith*, Proc. Chem. Soc. *1959*, 327; J. Chem. Soc. *1960*, 4791.

[81] *S. Farid*, Chem. Commun. 1268 (1967).

[82] *D. Bryce-Smith* and *A. Gilbert*, Chem. Commun. *1968*, 1701.

[83] Such experimental results are discussed in ref. [1].

[84] *D. N. Reinhoudt, H. C. Volger, C. G. Kouwenhoven, H. Wynberg*, and *R. Helder*, Tetrahedron Lett. *1972*, 5269.

[85] *K. C. Brannock, R. D. Bupitt, V. W. Goodlett*, and *J. G. Thweatt*, J. Org. Chem. *28*, 1464 (1963).

[86] *O. L. Chapman, D. T. Pasto, G. W. Borden*, and *A. A. Griswold*, J. Amer. Chem. Soc. *84*, 1220 (1962).

[87] *R. Breslow, J. Napierski*, and *A. H. Schmidt*, J. Amer. Chem. Soc. *94*, 5906 (1972).

[88] *R. Gompper, E. Kutter*, and *H. Knast*, Angew. Chem. *79*, 147 (1967), Angew. Chem. internat. Edit. *6*, 171 (1967); *R. Gompper, H. U. Wagner*, and *E. Kutter*, Chem. Ber. *101*, 4123, 4144 (1968); *R. Gompper* and *G. Seybold*, Angew. Chem. *83*, 45 (1971); Angew. Chem. internat. Edit. *10*, 68 (1971).

[89] Such experimental results are discussed in Ref. [1]. See also: *W. G. Dauben, M. S. Kellogg, J. I. Seeman, N. D. Vietmeyer*, and *P. H. Wendschuh*, Pure Appl. Chem. *33*, 197 (1973).

[90] *G. Quinkert*, Pure Appl. Chem. *33*, 285 (1973); *G. Quinkert*, Angew. Chem. *84*, 1157 (1972); Angew. Chem. internat. Edit. *11*, 1072 (1972); *J. Griffiths* and *H. Hart*, J. Amer. Chem. Soc. *90*, 5296 (1968).

[91] *O. L. Chapman* and *G. W. Borden*, J. Org. Chem. *26*, 4185 (1961); *O. L. Chapman, D. J. Pasto, G. W. Borden*, and *A. A. Griswold*, J. Amer. Chem. Soc. *84*, 1220 (1962); *K. E. Hine* and *R. F. Childs*, J. C. S. Chem. Commun. *1972*, 145; *H. Hart*, Pure Appl. Chem. *33*, 247 (1973).

[92] The possibility of *cis-trans* photoisomerization of the cycloheptadienone followed by conrotatory ring closure to yield the *cis* based bicyclic product should not be lightly dismissed.

[93] This is discussed in Ref. [1].

[94] *D. W. Turner*, Progr. Phys. Org. Chem. *4*, 31 (1966).

[95] *N. S. Hush* and *J. A. Pople*, Trans. Faraday Soc. *51*, 600 (1955).

[96] *J. A. Berson* and *G. L. Nelson*, J. Amer. Chem. Soc. *89*, 5303 (1967); *J. A. Berson*, Accounts Chem. Res. *1*, 152 (1968).

[97] *J. A. Berson* and *G. L. Nelson*, J. Amer. Chem. Soc. *92*, 1096 (1970).

[98] *F. G. Klärner*, Tetrahedron Lett. *1971*, 3611.

[99] *R. C. Cookson* and *J. E. Kemp*, Chem. Commun. *1971*, 385.

[100] *J. A. Berson* and *R. Holder*, cited in Ref. [23].

[101] *K. Schaffner*, Pure Appl. Chem. *33*, 329 (1973).

[102] See also: *R. F. C. Brown, R. C. Cookson*, and *J. Hudec*, Chem. Commun. *1967*, 823; *R. C. Cookson, V. N. Gogte, J. Hudec*, and *N. A. Mirza*, Tetrahedron Lett. *1965*, 3955.

[103] *R. L. Cargill, B. M. Gimarc, D. M. Pond, T. Y. King, A. B. Sears*, and *M. R. Wilcott*, J. Amer. Chem. Soc. *92*, 3809 (1970).

[104] See Ref. [1].

[105] However, see: *J. A. Berson*, Accounts Chem. Res. *1*, 152 (1968).

[106] *K. J. Crowley*, Proc. Chem. Soc. *1964*, 17; *R. Srinivasan*, J. Amer. Chem. Soc. *84*, 3982 (1962).

[107] *R. M. Roberts* and *R. G. Landolt*, J. Amer. Chem. Soc. *87*, 2281 (1965); *E. F. Kiefer* and *C. H. Tanna, ibid. 91*, 4478 (1969); *E. F. Kiefer* and *J. Y. Fukunaga*, Tetrahedron Lett. *1969*, 773.

[108] *W. G. Dauben* and *W. T. Wipke*, Pure Appl. Chem. *9*, 539 (1964).

[109] *G. W. Wheland:* Advanced Organic Chemistry. 3. Edit. Wiley, New York 1960; *J. Hine*, J. Org. Chem. *31*, 1236 (1966); J. Amer. Chem. Soc. *88*, 5525 (1966).

[110] *L. E. Friedrich* and *G. B. Schuster*, J. Amer. Chem. Soc. *93*, 4602 (1971).

[111] *H. M. Frey* and *R. K. Solly*, Trans. Faraday Soc. *64*, 1858 (1968); *E. Foster, A. C. Cope*, and *F. Daniels*, J. Amer. Chem. Soc. *69*, 1893 (1947); *H. M. Frey* and *D. C. Montague*, Trans. Faraday Soc. *64*, 2369 (1968).

[112] *E. S. Lewis, J. T. Hill*, and *E. R. Newman*, J. Amer. Chem. Soc. *90*, 662 (1968).

[113] *W. Cooper* and *W. D. Walters*, J. Amer. Chem. Soc. *80*, 4220 (1958); *H. H. Freedman, G. A. Doorakian*, and *V. R. Sandel, ibid. 87*, 3019 (1965).

[114] *G. S. Hammond*, Advan. Photochem. *7*, 373 (1969).

[115] These results are reviewed by *M. Ottolenghi*, Accounts Chem. Res. *6*, 153 (1973).

[116] *S. P. McGlynn, T. Azumi*, and *M. Kinoshita:* Molecular Spectroscopy of the Triplet State. Prentice-Hall, Englewood Cliffs, N. J. 1969.

[117] That is, stereoselectivity which is predicted from the theoretical considerations reported in this paper.

[118] *H. P. Kaufmann* and *A. K. SenGupta*, Liebigs Ann. Chem. *681*, 39 (1965).

[119] *W. Metzner*, Tetrahedron Lett. *1968*, 1321.

[120] *O. L. Chapman, T. H. Koch, F. Klein, P. J. Nelson*, and *E. L. Brown*, J. Amer. Chem. Soc. *90*, 1657 (1968).

[121] *H. D. Scharf*, Tetrahedron Lett. *1967*, 4231. This reaction occurs also in the absence of sensitization.

[122] See *A. Zweig*, Pure Appl. Chem. *33*, 389 (1973).

[123] In addition to our work, there have been two general theoretical approaches to photochemical reactions: *R. C. Dougherty*, J. Amer. Chem. Soc. *93*, 7187 (1971); *J. Michl*, Mol. Photochem. *4*, 243, 257, 287 (1972).

[124] *L. V. Smirnov-Zamkov* and *G. A. Piskovitina*, Ukr. Khim. Zh. *28*, 531 (1962).

[125] *M. J. S. Dewar* and *R. C. Fahey*, J. Amer. Chem. Soc. *85*, 3645 (1963).

[126] *M. L. Poutsma*, J. Amer. Chem. Soc. *87*, 2161 (1965).

[127] *R. K. Summerbell* and *H. E. Lunk*, J. Amer. Chem. Soc. *79*, 4802 (1957).

[128] *P. G. Gassman*, Accounts Chem. Res. *4*, 128 (1971); *A. Cairncross* and *E. P. Blanchard, Jr.*, J. Amer. Chem. Soc. *88*, 496 (1966).

[129] *H. H. Wasserman, A. J. Solodar*, and *L. S. Keller*, Tetrahedron Lett. *1968*, 5597; *L. Friedman, R. J. Osiewicz*, and *P. W. Rabideau*, Tetrahedron Lett. *1968*, 5735.

[130] The theory of diradicals is persuasively developed by *L. Salem* and *C. Rowland*, Angew. Chem. *84*, 86 (1972); Angew. Chem. internat. Edit. *11*, 92 (1972).

[131] The term diradicaloid is taken to mean a diradical with varying degrees of charge separation.

[132] These thermochemical calculations refer to extreme nonpolar cycloreversions, such as cyclobutane decomposition, which can be assumed to proceed *via* diradical intermediates. See *H. E. O'Neal* and *S. W. Benson*, J. Phys. Chem. *72*, 1866 (1968).

[133] *G. Klopman*, J. Amer. Chem. Soc. *90*, 223 (1968).

[134] For an admonition regarding the possible inadequacies of simple quantum mechanical schemes in treating diradical interactions, see: *L. M. Stephenson, T. A. Gibson*, and *J. I. Brauman*, J. Amer. Chem. Soc. *95*, 2849 (1973).

[135] *R. S. Mulliken* and *W. B. Person:* Molecular Complexes. Wiley-Interscience, New York 1969.

[136] *H. C. Longuet-Higgins* and *J. N. Murrell*, Proc. Phys. Soc. (London) *A 68*, 601 (1955); *J. N. Murrell*, J. Chem. Phys. *37*, 1162 (1962); *J. N. Murrell:* The Theory of Electronic Spectra of Organic Molecules. Methuen, London 1963.

[137] For interesting accounts, see also *H. Suzuki:* Electronic Absorption Spectra and Geometry of Organic Molecules. Academic Press, New York 1967; *S. P. McGlynn, L. G. Vanquickenborne, M. Kinoshita*, and *D. G. Carroll:* Introduction to Applied Quantum Chemistry. Holt, Rinehart and Winston, New York 1972.

Kinetics and Mechanism of Radical Polymerization

By Peter Mehnert[*]

Low molecular reactions are frequently accompanied by side reactions producing a whole spectrum of by-products whose removal in purification operations generally causes little difficulty because the major and side products usually differ sufficiently in their properties. Hence detailed kinetic studies in low molecular chemistry can claim industrial interest only insofar as they aim to reduce the rate of formation of side products. The situation is completely different in polymer chemistry, where the terms major and side product no longer apply. Instead, one obtains mixtures of similar and/or isomeric molecules which differ so little with regard to molecular weight and structure that resolution into pure substances or isolation of pure substances becomes practically impossible. However, since all partial reactions exert a direct influence on the product spread, *i.e.* the composition and properties of a product mixture are modified by any change in operating conditions, detailed kinetic analyses embracing all relevant partial reactions are an essential prerequisite for the production of defined polymeric products on any scale. This progress report illustrates the importance of kinetics for radical polymerization with the aid of selected examples.

1. Introduction

A series of industrial processes affording products of various qualities are available for radical polymerization, *viz.* solution polymerization, emulsion polymerization, suspension polymerization, and bulk polymerization. The present report deals exclusively with bulk polymerization, whose industrial importance has increased enormously in recent years.

Apart from the case of styrene, which undergoes spontaneous transformation into high molecular compounds, bulk polymerization requires only very small amounts of an auxiliary compound to initiate the polyreaction. This advantage of bulk polymerization, which requires no further additives (such as solvents, controllers, emulsifiers *etc.*) and consequently yields exceptionally pure polymeric products, is counterbalanced by the particularly difficult technical problem of removing the extremely high heats of polymerization amounting to about 100 kJ per mol of monomer.

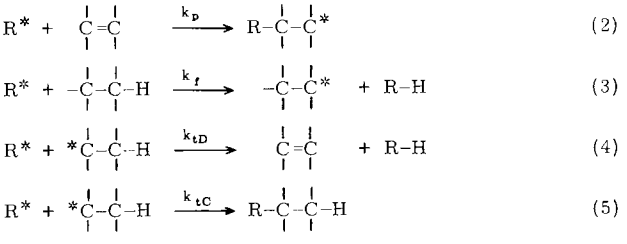
Those substances which trigger off a polyreaction are termed initiators. The initiators generally used in radical polymerization are peroxides or azo compounds, *e.g.* azodiisobutyronitrile AIBN whose fragments become components of the macromolecules [eq. (1)]. The initiators can fragment thermolytically

$$NC{-}C(CH_3)_2{-}N{=}N{-}C(CH_3)_2{-}CN \xrightarrow{k_i} 2\,{}^*C(CH_3)_2{-}CN + N_2 \quad (1)$$

(thermally induced polymerization) or photolytically (photosensitized polymerization).

Radical polymerization is characterized by the high reactivity of the active polymeric radicals combined with a pronounced non-specificity of reaction: they react both with molecules and with other radicals, by addition and by substitution. In polymer chemistry these reactions are known as: chain propagation (2), chain transfer (3), disproportionating termination (4), and combinational termination (5); R* corresponds to a polymer radical, *e.g.* $^*CHX{-}CH_2{+}CHX{-}CH_2{\rightarrow}_n H$.

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$$R^* + \text{C=C} \xrightarrow{k_p} R{-}C{-}C^* \quad (2)$$

$$R^* + {-}C{-}C{-}H \xrightarrow{k_f} {-}C{-}C^* + R{-}H \quad (3)$$

$$R^* + {}^*C{-}C{-}H \xrightarrow{k_{tD}} C{=}C + R{-}H \quad (4)$$

$$R^* + {}^*C{-}C{-}H \xrightarrow{k_{tC}} R{-}C{-}C{-}H \quad (5)$$

Since the starting materials (saturated molecules, radicals, olefins) are partly regenerated in these reactions, the events occurring are extremely complex and finer details still elude description, especially since material factors play a considerable role. Some principle features of importance in the bulk polymerization of vinylic and acrylic compounds in the liquid phase are reported below.

2. Chain Propagation

By far the most important reaction mentioned in Section 1 is the addition of monomer molecules to polymer radicals [eq. (2)] for it determines the microstructure of the polymer chain. This reaction is uniform in that, in the case of monosubstituted and geminally disubstituted olefins, practically only head-to-tail linkages occur which lead to a C—C chain comprising planar zig-zag sections and helical sections of various lengths and joined together in some kind of statistical sequence.

Each linkage step, however, also generates a new center of asymmetry and thus determines the configuration (D or L) of a further asymmetrical C atom. If an irregular D-L sequence is obtained, as in radical polymerization, then the number of possible stereoisomers for a fairly long molecule is greater than the number of molecules of this chain length that can ever be synthesized! Given a mean degree of polymerization of $\bar{P}_n = 10^3$, a production figure of 10^7 t/a corresponds to about 10^{32} macromolecules per year; however, just the vinyl polymer molecules having 1000 basic units amount to 2^{1000} ($= 10^{301}$) stereoisomers.

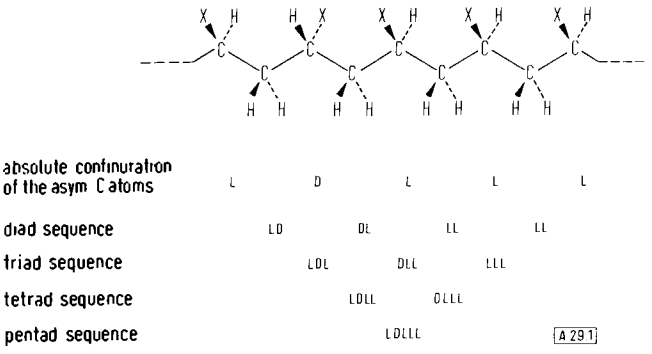


Fig. 1. Section of a head-to-tail linked vinyl polymer bearing the substituent X; its tacticity is denoted by the relative frequency of individual sequences.

For this reason, structural information pertaining to high polymers is usually restricted to the relative frequency of the various stereochemical arrangements in individual sequences (Fig. 1): stipulation of the relative frequency of the three diad sequences (DD), (DL), and (LL), the six triad sequences [eqs. (6)—(8)], the ten tetrad sequences, *etc.* *Natta* coined the term tacticity for this stereoisomerism, and *e.g.* (mm), (mr), and (rr) also designate the relative frequencies

$$(mm) = (DDD) + (LLL) \quad (6)$$

$$(mr) = (DDL) + (DLL) \quad (7)$$

$$(rr) = (DLD) + (LDL) \quad (8)$$

of the isotactic [eq. (6)], the heterotactic [eq. (7)], and the syndiotactic triads [eq. (8)], the symbols m and r being taken from the terms "meso" and "racemic". The significance of the tacticity becomes clear from the following example: whereas polystyrene of tacticity (mm)=1; (mr)=(rr)=0 has a melting point of 230 °C, this value drops to 100 °C for a polystyrene of tacticity (mr)=0.5; (mm)=(rr)=0.25.

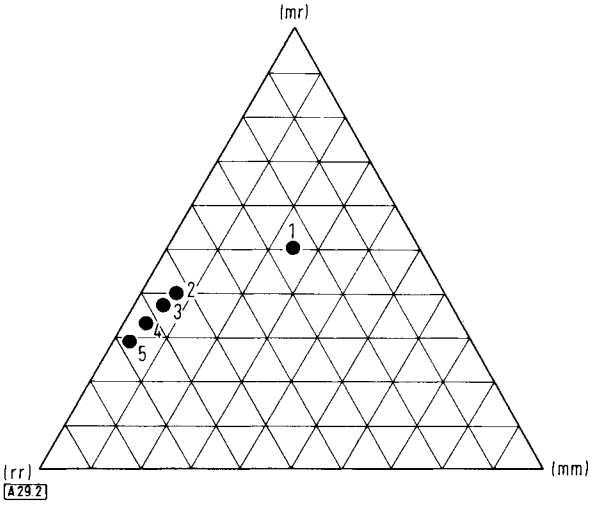


Fig. 2. Tacticity of polymers prepared by radical methods at 50 °C; (mm), (mr), and (rr) denote the relative frequencies of iso-, hetero-, and syndiotactic triads, respectively. 1 = poly(vinyl acetate) [3], poly(methyl acrylate) [4], polyacrylonitrile [5], poly(vinyl bromide) [6], poly(vinyl formate) [7], poly(vinyl chloride) [6, 8, 9]; 2 = poly(methyl methacrylate) [7, 10—12]; 3 = poly(methyl α-chloroacrylate) [13]; 4 = poly(*n*-butyl methacrylate) [14]; 5 = poly(glycidyl methacrylate) [15].

The frequency of the arrangements can best be established by high resolution nuclear magnetic resonance spectroscopy[1].

Figure 2 illustrates the tacticity of several polymers prepared by radical methods[2]. Vinyl polymers are seen to possess a highly regular structure; the relative frequencies of the triad sequences are in the ratio (mm) : (mr) : (rr) = 0.25 : 0.50 : 0.25, whereas polymers obtained from geminally disubstituted olefins exhibit a considerably higher syndiotactic component (rr). The size of substituents apparently also plays a role in methacrylic polymers.

Apart from this pronounced effect of substituent size on the tacticity of polymers produced by radical methods, a minor influence of the polymerization temperature has also been ascertained, which can be expressed in an Arrhenius equation [eq. (9)]. However, this influence is unimportant [E in eq.

$$((DD) + (LL))/(DL) = k\exp(-E/RT) \quad (9)$$

(9) is at most 4 kJ mol^{-1}] so that the polymerization temperature cannot be employed to significantly modify the tacticity of a polymeric product. Whether an Arrhenius representation of the temperature effect is in fact at all justified cannot generally be decided on the basis of a few measurements since it is absolutely essential to investigate a very large temperature range in the case of such small temperature gradients. *Kador* and *Mehnert*[3] have carried out measurements in the range −60... +200 °C and were unable to detect any influence of the polymerization temperature on the tacticity of, *e.g.*, poly(vinyl acetate).

Determination of the relationship between the frequencies and kinetic reaction parameters proves to be fairly complicated since it must be assumed that the addition reaction is influenced both by directly preceding linkages and by the various conformational states of the radical chain end. One therefore proceeds by setting up several reaction models and examining each one by comparison with the experimentally determined sequences. Agreement indicates that the model may be correct, while non-agreement definitely rules it out.

As an example, let us examine a reaction model which accounts for the two immediately preceding additions (...DD, ...DL, ...LD, or LL) and three conformational states ($i = 1, 2, 3$) of the radical chain end, *i.e.* for which a total of twelve different forms of the polymer radical are to be considered. Since each form offers two possible addition modes (D or L), the tacticity is determined by eqs. (10)—(12)[2].

$$(mm) = \Sigma\rho_{DD,i}\cdot\psi_{DD,D} + \Sigma\rho_{LL,i}\cdot\psi_{LL,L} \quad (10)$$

$$(rr) = \Sigma\rho_{DL,i}\cdot\psi_{DL,D} + \Sigma\rho_{LD,i}\cdot\psi_{LD,L} \quad (11)$$

$$(mr) = 1 - (mm) - (rr) \quad (12)$$

$\rho_{DD,i} = [R_{DD,i}]/[R]$ = relative concentration of the polymer radicals present in DD form *etc.*; $\psi_{DD,D} = (k_p(DD_iD)/(k_p(DD_iD) + k_p(DD_iL))$ = probability of formation of an asymmetric C atom of configuration D on addition of a monomer molecule to a polymer radical having the form DD_i, *etc.*

The manner in which these equations can be simplified, *i.e.* which terms can be neglected, which forms are present in equal concentrations, and which reaction probabilities are equal, as well as the question whether a high syndiotactic content is due primarily to differences in conformational state populations or differing reaction probabilities will be discussed later[16-18]. Solution of this problem will require further highly precise NMR studies in order to better understand the statistical relationship between the frequencies of the sequences, as well as extensive ESR investigations to provide information

about the the conformational states of the end of the radical chain.

Attempts have also been made to glean information about tacticity from polymer transition reactions. Thus *Messmer* and *Mehnert*[19,20] observed the intramolecular cyclization tendency of neighboring substituents to form hexacyclic systems and compared radical-polymerized polyisopentenone and polybutenone with purely syndiotactic 1,2-polybutadiene produced by an ionic process.

3. Polymer-Forming Reactions

At low conversions the reaction scheme (1)—(5) of initiated homogeneous polymerization becomes eqs. (13)—(17), which are presented in conventional abbreviated form. R_r and P_r represent specified polymer radicals R* and polymer molecules P. The subscript r indicates the number of monomeric units (fundamental units, structural units) which each of the particles contains, M signifies a monomer molecule. The rate constants

$$S \xrightarrow{k_i} 2R_1 \tag{13}$$

$$R_r + M \xrightarrow{k_p} R_{r+1} \tag{14}$$

$$R_r + M \xrightarrow{k_f} P_r + R_1 \tag{15}$$

$$R_r + R_{r'} \xrightarrow{k_{tD}} P_r + P_{r'} \tag{16}$$

$$R_r + R_{r'} \xrightarrow{k_{tC}} P_{r+r'} \tag{17}$$

at 20 °C are generally of the order of $k_i(\text{AIBN}) = 10^{-7}\,s^{-1}$; $k_p = 10^{+2}$, k_f 10^{-2}, $k_t = 10^{+7}$ mol^{-1} l s^{-1}. The polymer formation reactions are represented by eq. (15)—(17). Eq. (18) for the polymerization rate v_p can be derived from eq. (14). The change in radical concentration is given by eq. (19) or its integrated form [eq. (20)]. As seen from eq. (20), after a short reaction time the function $\tanh(2k_i[S](k_{tD}+k_{tC}))^{0.5}t \simeq 1$; hence the initial rate after this short induction period is given by eq. (21).

$$v_p \equiv k_p[M]\Sigma[R_r] \tag{18}$$

$$d\Sigma[R_r]/dt = 2k_i[S] - (k_{tD} + k_{tC})(\Sigma[R_r])^2 \tag{19}$$

$$\Sigma[R_r] = (2k_i[S]/(k_{tD} + k_{tC}))^{0.5} \tanh(2k_i[S](k_{tD} + k_{tC}))^{0.5}t \tag{20}$$

$$v_i \equiv 2k_i[S] = (k_{tD} + k_{tC})(\Sigma[R_r])^2 = ((k_{tD} + k_{tC})/k_p^2)(v_p/[M])^2 \tag{21}$$

Although the scheme (13)—(17) is fairly simple, the time-dependent expressions for the concentrations $[R_1]$, $[R_r]$, and $[P_r]$ are fairly complicated. Introduction of the symbols H and K [eqs. (25) and (26)] into eqs. (21)—(24) yields eqs. (27) and (28), and hence, after summation over all r, the general rate equation (29) for formation of the polymeric products

$$d[R_1]/dt = 2k_i[S] + k_f[M]\sum[R_r] - k_f[M][R_1] - k_p[M][R_1] - (k_{tD} + k_{tC})[R_1]\sum[R_r] \simeq 0 \tag{22}$$

$$d[R_r]/dt = k_p[M][R_{r-1}] - k_f[M][R_r] - k_p[M][R_r] - (k_{tD} + k_{tC})[R_r]\sum[R_r] \simeq 0 \tag{23}$$

$$d[P_r]/dt = k_f[M][R_r] + k_{tD}[R_r]\sum[R_r] + 0.5k_{tC}\sum_{h=1}^{h=r-1}[R_h][R_{r-h}] \tag{24}$$

$$H \equiv k_f/k_p + ((k_{tD} + k_{tC})/k_p^2)(v_p/[M]^2) \tag{25}$$

$$K \equiv 0.5(k_{tC}/k_p^2)(v_p/[M]^2) \tag{26}$$

$$[R_r] = H\cdot(1+H)^{-r}\Sigma[R_r] = H\cdot e^{rH}\cdot\Sigma[R_r] \tag{27}$$

$$d[P_r]/dt = v_p\cdot H\cdot e^{-rH}\cdot(H - K(2 - rH)) \tag{28}$$

$$d\Sigma r^i[P_r]/dt = v_p\cdot H^{-i}\cdot(H - K(1-i))\cdot\Gamma(1+i) \tag{29}$$

and the Poisson distributions [eqs. (30) and (31)] representing the molecular weight distributions of the polymer molecules and polymer radicals (i,j = positive real numbers including zero). Equations (30) and (31) are likewise generally valid[21], *i.e.* for all distributions (including fractional values of i) and in the presence of all three polymer formation reactions, $i=0$ corresponds to the frequency distribution and $i=1$ to the mass distribution of the polymer particles.

$$\frac{r^i[P_r]}{\sum r^i[P_r]} \approx \frac{d\,r^i[P_r]/dt}{d\sum r^i[P_r]/dt} = \frac{H}{\Gamma(1+i)}\,\frac{(rH)^i}{e^{rH}}\cdot\frac{H - K(2-rH)}{H - K(1-i)} \tag{30}$$

$$\frac{r^i[R_r]}{\sum r^i[R_r]} = \frac{H}{\Gamma(1+i)}\cdot\frac{(rH)^i}{e^{rH}} \tag{31}$$

Frequent use of made of the mean degrees of polymerization [eq. (32)], which are much more readily accessible experimentally, and $\bar{P}$ is designated as number average $\bar{P}_n$ for $i=1$; $j=0$, as weight average $\bar{P}_w$ for $i=2$; $j=1$, as z-average P_z for $i=3$; $j=1$, and as viscosity average $\bar{P}_\eta$, which is related to the Staudinger index $[\eta] = K_\eta(\bar{P}_\eta)^\alpha$, for $i = 1+\alpha$; $j=1$. The non-uniformity NU is sometimes also used as parameter for the molecular weight distribution of a polymeric product [eq. (33)]; it lies between 0.5 and 1.0, provided that the reaction course corresponds to eqs. (13)—(17).

$$(\bar{P})^{i-j} \equiv \frac{\sum r^i[P_r]}{\sum r^j[P_r]} \approx \frac{d\sum r^i[P_r]/dt}{d\sum r^j[P_r]/dt} = \frac{H - K(1-i)}{H - K(1-j)}\cdot\frac{\Gamma(1+i)}{\Gamma(1+j)}\cdot H^{j-i} \tag{32}$$

$$NU \equiv (\bar{P}_w/\bar{P}_n) - 1 = 1 - 2(K/H)^2 \tag{33}$$

Equations (27)—(33), which are each written in a general manner[21], clearly show that not only the yield, reaction rate, *etc.* but also the properties of polymers (*i.e.*, in particular, the mean degree of polymerization and molecular weight distribution) are determined by the reaction conditions (primarily temperature, and concentration of initiator and monomer). The experimentally accessible quantities v_p (from conversion/time curves determined by gravimetry or dilatometry) and $\bar{P}$ (from molecular weight determinations by osmometric, light scattering, viscosity, terminal group methods or with an ultracentrifuge) and v_i (from initiator decomposition) always yield only the ratios k_f/k_p and k_t/k_p^2, as is underlined by eqs. (21), (25), and (26). Individual determinations of rate constants can be performed using a method developed by *Chapman et al.*[22] and introduced into polymerization kinetics by *Melville*[23], *viz.* the method of intermittent irradiation in which a thermally induced polymerization is reinforced at equidistant intervals by photosensitized polymerization. Three separate experiments furnish one polymerization rate each: in the dark $(v_p)_{dark}$; on continuous irradiation $(v_p)_{cont}$; on intermittent irradiation $(v_p)_{int}$. If t_l and t_d represent the length of the light and dark period respectively, then the expression due to *Mehnert*[24] (34) affords the ratio k_t/k_p, and it then proves possible to determine k_f, k_p, and k_t.

$$\cosh\frac{k_t A}{k_p[M]} = G^2\cdot\cosh\frac{k_t(B+C)}{k_p[M]} + (1-G^2)\cdot\cosh\frac{k_t(B-C)}{k_p[M]} \tag{34}$$

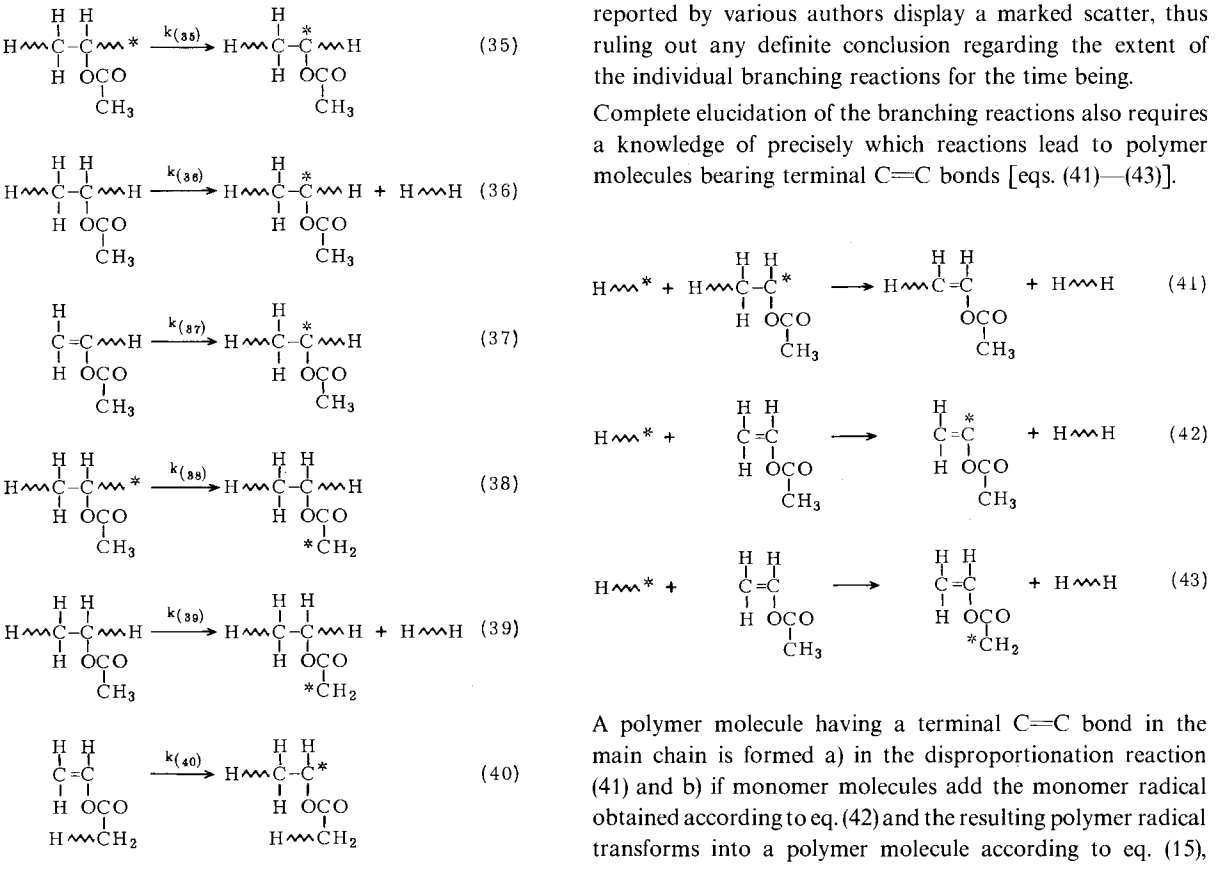
$$A \equiv (t_l + t_d)(v_p)_{int};\ B \equiv t_l(v_p)_{cont};\ C \equiv t_d(v_p)_{dark};\ G \equiv \cosh\ln\sqrt{(v_p)_{cont}/(v_p)_{dark}}$$

4. Polymer Branching Reactions

The relationships (22)—(23) apply strictly only to the starting conditions, *i.e.* for conversions $C \rightarrow 0\,\%$, since both the falling radical concentration (due to initiator consumption) and the falling monomer concentration have an increasing effect on the molecular weight distribution (and derived quantities) as conversion progresses. Moreover, the very slight, and generally negligible, dependence of the rate constants upon chain length leads to a minor shift in the molecular weight distribution, shorter molecules being disfavored.

However, polymer branching reactions exert a far greater effect upon these functions, and thus upon the properties of the products. Polymer branching reactions are secondary reactions through which polymer radicals and polymer molecules participate in the reaction course such that branched polymer particles are formed; initiated vinyl acetate polymerization is a typical example [eqs. (35)—(40)].

Polymer radicals react a) intramolecularly by substitution [eqs. (35) and (38)], b) with polymer molecules by substitution [eqs. (36) and (39)], and c) with polymer molecules bearing



terminal C=C bonds by addition [eqs. (37) and (40)]; since numerous monomer molecules add to the branching points, there arise main-chain-branched [eqs. (35)—(37)] and ester-branched [eqs. (38)—(40)] polymer radicals which subsequently furnish correspondingly branched polymer molecules according to eq. (15), (16), or (17). Polymer branching thus illustrates the case of a reactant yielding the same product *via* several different pathways. The reaction sequences can only be resolved with the aid of kinetic measurements and comparison with simplifying models.

Experimental study of polymer branching[25-32] has been limited almost exclusively to poly(vinyl acetate); generally speaking the rise in the mean degree of polymerization was determined as a function of the conversion for a given initial polymerization rate. Some researchers have also hydrolyzed the polymeric product to poly(vinyl alcohol) and subsequently reacetylated it to poly(vinyl acetate). This procedure cleaved the ester-branched polymer molecules and thus reduced the mean degree of polymerization. The results are summarized in Table 1. As seen from the Table the relative rate constants

Table 1. Relative rate constants of polymer branching reactions in vinyl acetate polymerization; the rate constants of the substitution reactions (36) and (39) were based on k_t, and those of the addition reactions (37) and (40) on k_p.

T[°C]	$\frac{k_{(36)}}{k_t}$	$\frac{k_{(39)}}{k_t}$	$\frac{k_{(37)}}{k_p}$	$\frac{k_{(40)}}{k_p}$	Ref.
70	0.6	0.3	0	1.0	[25]
60	0.93		0.8		[26]
60	0.63		0.8		[29]
60	1.0		0.66		[30]
60	1.4	0.6	0	0.75	[32]

reported by various authors display a marked scatter, thus ruling out any definite conclusion regarding the extent of the individual branching reactions for the time being.

Complete elucidation of the branching reactions also requires a knowledge of precisely which reactions lead to polymer molecules bearing terminal C=C bonds [eqs. (41)—(43)].

A polymer molecule having a terminal C=C bond in the main chain is formed a) in the disproportionation reaction (41) and b) if monomer molecules add the monomer radical obtained according to eq. (42) and the resulting polymer radical transforms into a polymer molecule according to eq. (15), (16), or (17); a polymer molecule having a terminal C=C bound to the principal chain *via* an ester bridge if the monomer radical formed as shown in eq. (43) reacts in the manner just described.

While the occurrence of reaction (43) and its secondary reactions is beyond dispute, *Nozakura et al.*[32] assume that reaction (42) can be neglected in comparison with the competing reaction (43). The reaction sequence (41), (37) was first proposed by *Mehnert*[31,33,34], who found for poly(vinyl acetate) that the extent of ester branching (which accounts for at most 75—80 % of the total branching[35]) falls with decreasing

degree of polymerization, whereas the mean degree of overall branching $\bar{Z}$ ($\bar{Z}$ = number of branches per monomer unit) increases.

As seen from eqs. (25) and (32), the mean degree of polymerization $\bar{P}$ decreases when H, and thus the polymerization rate v_p, increases. In other words, at a low degree of polymerization the proportion of termination reactions in polymer formation increases, and hence also the rate of formation of terminal C=C in the principal chain according to eq. (41) (termination by disproportionation). Consequently, at high conversions the rate of formation of main-chain-branched polymer molecules according to eq. (37) will also be higher. Since this branching cannot be determined by hydrolysis/reacetylation, the interpretation is in accord with experimental findings. That termination of vinyl acetate polymerization occurs by disproportionation had already been established by *Funt* and *Pasika*[36]. Thus, contrary to previous thinking, the overall degree of branching $\bar{Z}$ increases with decreasing degree of polymerization in polymers whose formation reaction is predominantly disproportionating termination [see eqs. (4) and (16)]; according to eq. (44) $\bar{P}_n$ and $\bar{Z}$ depend only upon the conversion C and upon k_{tC}/k_{tD} and k_f/k_p.

$$(\bar{P}_n)^{-1} = (k_f/k_p)(\ln(1-C))(1-(1/C)-N)-(N\bar{Z}) \quad (44)$$
$$N \equiv (C-(1+(k_{tC}/k_{tD}))\ln(1-C))/(C+\ln(1-C))$$

5. Spontaneous Polymerization

Some monomers, especially styrene and its derivatives, form polymers without addition of initiators; they polymerize spontaneously and can only be stabilized by addition of inhibitors. The mechanism of this spontaneous transformation is likewise of a radical kind and has only recently been elucidated.

Let us first consider the question whether a purely "molecular mechanism" [eqs. (45) and (46)], a series of Diels-Alder additions without reverse reactions, can actually give rise to polymers. Integration of the differential equation (47) derived from eqs. (45) and (46) and insertion of various numerical values into the integrated equation yields the values listed

$$M + M \xrightarrow{k_{(45)}} P_2 \quad (45)$$

$$P_r + M \xrightarrow{k_{(46)}} P_{r+1} \quad (46)$$

$$-d[M]/d\textstyle\sum[P_r] = 2 + 2(k_{(46)}/k_{(45)})(\sum[P_r]/[M]) \quad (47)$$

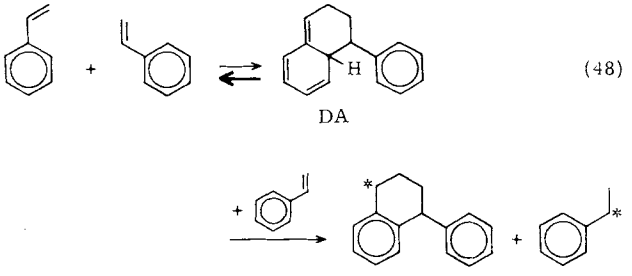
in Table 2[37]. It is immediately apparent from the figures that the initiation and propagation reactions must be completely different in character ($k_{(46)} \gg k_{(45)}$) if macromolecules

Table 2. Mean degrees of polymerization $\bar{P}_n = C[M]_0/\sum[P_r]$ calculated from eqs. (45)–(47) ("molecular mechanism") for various conversions $C \equiv 1-([M]/[M]_0)$ and ratios $k_{(46)}/k_{(45)}$. The subscript 0 indicates concentration at time $t = 0$.

C [%]	$k_{(46)}/k_{(45)}$	$\bar{P}_n$
100	10^8	1.4×10^4
1	10^8	1.0×10^3
100	10^4	1.4×10^2
1	10^4	1.1×10^1
100	1	3.1

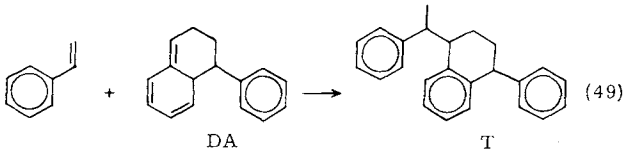
are to result, such as occurs even at very low conversions in the spontaneous polymerization of styrene.

Mayo[38] was the first to provide a satisfactory interpretation of the initial step occurring in the spontaneous polymerization of styrene. He formulated a Diels-Alder equilibrium between two styrene molecules and a trimolecular secondary reaction as the primary radical-generating reaction (48).



(48)

Kirchner[39] was able to confirm this two-step reaction; he found a significant isotope effect with regard to the rate and degree of polymerization of 2,4,6-trideuteriostyrene, which indicates that the angular hydrogen atom of the Diels-Alder adduct (DA) plays a key role in eq. (48). Moreover, *Buchholz* and *Kirchner*[40] demonstrated that the principal reaction of the Diels-Alder adduct is not regeneration of two monomer molecules but formation of the trimer (T) [eq. (49)] discovered by *Stein et al.*[41,42] in the spontaneous polymerization of styrene; four different stereoisomers are formed.



(49)

Quantitative elucidation of spontaneous styrene polymerization was accomplished by *Wiesner* and *Mehnert*[43,44]. They first performed a gas-chromatographic product analysis of all stable oligomers [*cis*- and *trans*-diphenylcyclobutane (CB), phenyltetralin (PhT), methylbenzyl(phenyltetralin) (T), phenyldihydronaphthalene (PhN)] arising during styrene polymerization and determined the kinetics of their formation. The same authors also completed a kinetic study on the inhibition of spontaneous polymerization with the 1,1-diphenyl-2-picrylhydrazyl radical[45,46] whose property of mild dehydrogenation fit it particularly well for the elucidation of radical mechanisms. The resulting conversion/time plots provided a basis for the first analog computer simulation of the overall reaction course; the initiation mechanism corresponds to the reaction scheme shown in Figure 3, and the Arrhenius equations (52) and (53) were obtained for the generation of the primary radicals [eqs. (50) and (51)].

$$M + M \xrightarrow{k_{DA}} DA \quad (50)$$

$$DA + M \xrightarrow{0.02 \cdot k_R} R_1 + R_2 \quad (51)$$

$$k_{DA} = 3 \times k_{CR} = 1.6 \times 10^6 \text{ mol}^{-1}\text{l s}^{-1} \exp(-102\text{ kJ mol}^{-1}/RT) \quad (52)$$

$$k_R = 25 \text{ mol}^{-1}\text{l s}^{-1} \exp(-40\text{ kJ mol}^{-1}/RT) \quad (53)$$

Once again the highly non-specific reactivity of the radicals becomes apparent: The "cage" radicals can both combine and dis-

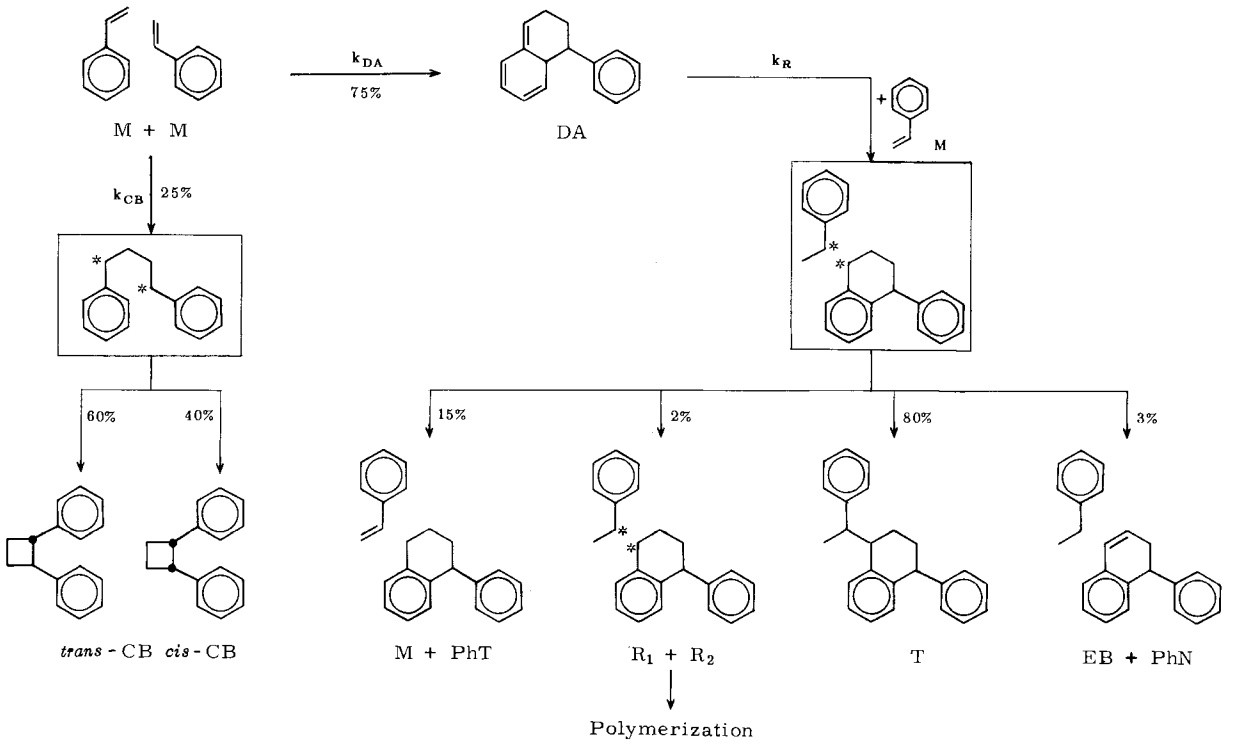


Fig. 3. Initiation mechanism of spontaneous styrene polymerization [44] EB = ethylbenzene; see text for other abbreviations.

proportionate (in two different ways), while some of them diffuse out of the "cage" and initiate the polyreaction. Reverse reactions and additional reaction steps postulated by other authors could not be detected by *Wiesner* and *Mehnert*. Moreover, all reactions obeyed the Woodward-Hoffmann rules.

In contrast to the initiation mechanism and its many side reactions, the polymerization process itself is surprisingly simple [eq. (54)—(56)]. As shown by *Wiesner* and *Mehnert*[47] on the basis of ultracentrifuge measurements, the non-uniformity of polystyrene is $NU = 0.5$ (at 30 °C), which according to eq. (33) is indicative of pure combination termination and

$$R_r + M \xrightarrow{k_p} R_{r+1} \tag{54}$$

$$R_r + R_{r'} \xrightarrow{k_{tC}} P_{r+r'} \tag{55}$$

$$k_{tC}/k_p^2 = 8.4 \times 10^{-8}\,\text{mol l}^{-1}\,\text{s}\exp(+68\,\text{kJ mol}^{-1}/RT) \tag{56}$$

rules out chain transfer to the oligomers. The overall scheme [eqs. (50), (51), (54), and (55)] shows the reaction to be second order with regard to monomer concentration [M] [eqs. (57) to (59)] once quasi-steady state concentrations have been established of R_r and DA; this result accords with the empirical rate law $v_p \sim [M]^2$ proposed by *Suess et al.*[48] and *Schulz et al.*[49] and confirmed by *Kirchner*[50].

$$d[DA]/dt = 0.5 \times k_{DA}[M]^2 - k_R[DA][M] \simeq 0 \tag{57}$$

$$d\Sigma[R_r]/dt = 2(0.02 \times k_R)[DA][M] - k_{tC}(\Sigma[R_r])^2 \simeq 0 \tag{58}$$

$$v_p \equiv k_p[M]\Sigma[R_r] = k_p \times (0.02 \times k_{DA}/k_{tC})^{0.5}[M]^2 \tag{59}$$

The induction period characterizing commencement of the spontaneous polymerization which was first reported by *Benoit*[51] and which affects both the rate and the degree of polymerization, comes about because the concentration of the Diels-Alder adduct, *i.e.* the "initiator of spontaneous polymerization", initially rises and only then assumes a quasi-steady value—in contrast to initiated polymerization where the initiator concentration is constant. At 30 °C the induction period amounts to 10^4 s[44] and the quasi-steady Diels-Alder adduct concentration $[DA]_{quas} = 5 \times 10^{-6}\,\text{mol l}^{-1}$[44]. Whereas $[DA]_{quas}$ is determined by the ratio k_{DA}/k_R, the length of the induction period depends solely upon k_R. Equation (60) shows the way in which the concentration of DA varies with time during the induction period.

$$[DA] = 0.5(k_{DA}/k_R)[M](1 - \exp(-k_R[M]t)) \tag{60}$$

As in initiated polymerization, the first step of spontaneous polymerization is rate determining. The rate constants of the subsequent reactions are considerably higher; the following ratios (61) apply at 30 °C:

$$k_{DA} : k_R : k_p : k_{tC} = 1 : 10^6 : 10^{13} : 10^{19} \tag{61}$$

6. Heterogeneous Polymerization

Some polymers are insoluble in their own monomers with the result that granular or gel-like precipitates are formed during bulk polymerization. This kind of polymerization, in which the monomer acts as precipitant for its own polymer is therefore designated heterogeneous polymerization. However, this phenomenological observation is not the only point in which such processes differ from homogeneous polymerization: the reaction kinetics also vary. Thus the conversion/time curves of heterogeneous polymerization resemble those of autocatalytic reactions with their marked accelerations at the commencement of reaction. Figure 4 compares the conversion/time curves for various kinds of polymerization. Disregarding the induction phase, the following experimentally confirmed rate laws are obtained for the rate of polymerization:

$$v_p \sim [M]\cdot[S]^{0.5}\cdot(k + [S]^{0.5}t) \quad (62)$$
$$v_p \sim [M]\cdot[S]^{0.5} \quad (63)$$
$$v_p \sim [M]^2 \quad (64)$$

for heterogeneously initiated bulk polymerization[52] eq. (62) from eqs. (73), (75), and (76); for homogeneously initiated bulk polymerization eq. (63) from eq. (21); and for homogeneous spontaneous bulk polymerization eq. (64) from eqs. (59).

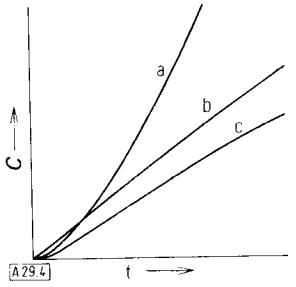


Fig. 4. Conversion/time curves (qualitative) for: a) heterogeneously initiated bulk polymerization of acrylonitrile; b) homogeneously initiated bulk polymerization of vinyl acetate; c) homogeneous spontaneous bulk polymerization of styrene.

The kinetics of heterogeneous polymerization of acrylonitrile were first studied by *Bamford* and *Jenkins*[53-55]. The empirical rate law $v_p \sim [S]^{0.9}$ found by these authors and since confirmed by other invcstigators (most recently by *Lewis* and *King*[56]) was derived qualitatively from the concept that a homogeneously generated polymer radical does not form polymer molecules according to eqs. (15)—(17) but first precipitates and continues to grow in a heterogeneous state at the same rate as monomer molecules can diffuse to the radical site incorporated in the polymer coil, a process subject to steadily increasing hindrance (radical inclusion theory[53-55]). Thus, bimolecular formation of polymer molecules does not occur, but instead chain propagation of a heterogeneous polymer radical gradually stagnates owing to the drop in the rate constant $k_{p(het)}$ with increasing chain length. Indeed, *Bamford* and *Jenkins* have demonstrated radical properties of the isolated polymeric product by ESR measurements[57] and decoloration tests with reddish-violet 1,1-diphenyl-2-picrylhydrazyl[58].

A comprehensive and quantitative kinetic analysis of bulk polymerization of acrylonitrile was first conducted by *Marquardt* and *Mehnert*[52,59-62], who were unable to confirm the rate law $v_p \sim [S]^{0.9}$ but found the expression (62) to apply. They developed an improved dilatometric technique for determining conversion/time curves of heterogeneous polymeriza-

$$S \xrightarrow{v_i} 2R\cdot \quad (65)$$
$$R_r(hom) + M \xrightarrow{k_p(hom)} R_{r+1}(hom) \quad (66)$$
$$R_r(hom) + R_s(hom) \xrightarrow{k_t} P_{r+s} \text{ or } P_r + P_s \quad (67)$$
$$R_r(hom) \xrightarrow{f\cdot v_i} R_r(het) \quad (68)$$
$$R_r(het) + M \xrightarrow{k_p(het)} R_{r+1}(het) \quad (69)$$

tion and employed a new method of evaluation. The result of their studies is summarized in the reaction scheme (65)—(69) for acrylonitrile.

This mechanism is based on the concept that chain propagation (66) is presumably considerably faster (the time τ between two additions is only $\tau = (k_p[M])^{-1} \approx 10^{-4}$ s) than the precipitation process (68) of polymer radicals initially growing in the homogeneous state, *i.e.* that by far the greater part of the polymer radicals R_r (hom) is transformed into polymer molecules in bimolecular termination reactions (67) which then precipitate, and that only a very small fraction f (f = polymer radical precipitation factor) of the polymer radicals becomes heterogeneous [eq. (68)]. The heterogeneous polymer radicals R_r (het) then continue to grow with a steady rate constant k_p (het) [eq. (69)] but do not participate significantly in termination reactions owing to their immobility. Presumably the branching reactions (35) and (36) take place. This simple interpretation has been backed up in several respects by *Marquardt* and *Mehnert*[52]. There result: eqs. (70) and (71) from eq. (65); eqs. (72) and (73) from eqs. (65), (67), and (71), taking account of eqs. (20) and (21); and eqs. (74) and (75) from eqs. (68) and (71). If eqs. (73) and (75) are inserted into eq. (76) and eq. (76) is then integrated, one obtains eq. (77) for $C = 1 - ([M]/[M]_0)$. This integrated rate equation (77) permits a very good description of the experimental results.

$$-d[S]/dt \equiv 0.5 \times v_i = k_i[S] \quad (70)$$
$$[S] = [S]_0 \exp(-k_i t) \quad (71)$$
$$d\Sigma[R_r(hom)]/dt = 2k_i[S](1-f) - k_t(\Sigma[R_r(hom)])^2 \quad (72)$$
$$\Sigma[R_r(hom)] \sim [S]^{0.5} \sim [S]_0^{0.5}\exp(-0.5 \times k_i t) \quad (73)$$
$$d\Sigma[R_r(het)]/dt \equiv fv_i = 2fk_i[S] = 2fk_i[S]_0 \times \exp(-k_i t) \quad (74)$$
$$\Sigma[R_r(het)] \sim [S]_0\cdot(1 - \exp(-k_i t)) \quad (75)$$

Y versus t plots of the experimental data are straight lines whose intersections with the ordinate are proportional to $[S]_0^{0.5}$ and whose slopes are proportional to $[S]_0^{1.0}$ (the subscript 0 signifies the concentration at $t = 0$). The first term in eq. (77) corresponds to chain growth of polymer radicals present in homogeneous form and the second to that of polymer radicals present in heterogeneous form. Since the

$$-d[M]/dt \sim v_p \equiv k_p(hom)[M]\sum[R_r(hom)] + k_p(het)[M]\sum[R_r(het)] \quad (76)$$

$$Y \equiv \frac{-\ln(1-C)}{1-\exp(-0.5 \times k_i t)} = k'[S]_0^{0.5} + k''[S]_0 t \quad (77)$$

latter are not subject to termination, their concentration increases with the reaction time t. The rate constants of steps (65)—(69) present in the constants k' and k'' in eq. (77) were found to be given by eqs. (78) and (79). The polymer radical precipitation factor f lies between 10^{-2} and 10^{-3} at 50 °C, and the rate constant k_p(het) predictably between 10^2 and 10^3 mol^{-1} l s^{-1}, *i.e.* in the same range as the values given for k_p(hom) in the literature. Further support for reactions (65)—(69) comes from work by *Bamford et al.*[63] who obtained a value for k_t/k_p^2 in the homogeneous solution polymerization of acrylonitrile at 60 °C which lies only 40 % above that determined by *Marquardt* and *Mehnert*[52] for bulk polymerization by a greatly improved method.

$$k_t/k_p^2(hom) = 7 \times 10^{-8} \text{ mol l}^{-1} \text{ s} \exp(+60 \text{ kJ mol}^{-1}/RT) \quad (78)$$
$$f\cdot k_p(het) = 3 \times 10^{+12} \text{ mol}^{-1} \text{ l s}^{-1} \exp(-80 \text{ kJ mol}^{-1}/RT) \quad (79)$$

Similar to the situation in spontaneous polymerization induction periods are measurable; here the length of the induction periods t_{IP} observed in heterogeneously induced polymeriza-

tion depends upon the initiator concentration: $t_{IP} \sim [S]_0^{-0.5}$. This experimental finding[52] also accords with the concept that the course of events at the commencement of reaction is determined solely by the contribution of homogeneous polymerization. *Marquardt* and *Mehnert*[52] derived this proportionality from scheme (13)—(17).

7. Precipitation Polymerization

On polymerization, methacrylonitrile behaves completely differently from acrylonitrile[65, 66]. In a well stirred reactor the conversion/time curves follow the same course as with homogeneously initiated bulk polymerization, except that induction periods occur whose length is proportional to $[S]_0^{-0.5}$.

This suggests that the bulk polymerization of methacrylonitrile is a homogeneous polymerization and no polymer radicals precipitate. Corroborating evidence is provided by the empirical rate law (63) found by several different authors[65–68]. The value of k_t/k_p^2 determined for the bulk polymerization is of the same order of magnitude as that for solution polymerization. The only justification for calling this kind of polymerization precipitation polymerization lies in the successive precipitation of "finished" polymer molecules owing to their limited solubility.

8. Two-Phase Polymerization

As shown by *Marquardt* and *Mehnert*[64, 65], a completely different picture results when the bulk polymerization of methacrylonitrile is carried out without stirring. Under such conditions a second AIBN/monomer/polymer phase II appears in which a homogeneous polymerization also occurs. Hence combination of eq. (80) and eq. (21) affords eq. (81) in which the total volume $V = V_I + V_{II}$.

$$v_p \equiv (V_I/V) \times k_{pI}[M]_I \Sigma[R_r]_I + (V_{II}/V) \times k_{pII}[M]_{II} \Sigma[R_r]_{II} \quad (80)$$

$$v_p = (V_I/V) \times (v_i k_p^2/k_t)_I^{0.5}[M]_I + (V_{II}/V) \times (v_i k_p^2/k_t)_{II}^{0.5}[M]_{II} \quad (81)$$

Indeed, on separation of the polymeric products by gel chromatography and ultracentrifugation, *Engel* and *Mehnert*[69] found a bimodal molecular weight distribution providing direct confirmation of the two-phase polymerization concept. If the reactor contents are well stirred no such bimodal distribution occurs[65]. Surprisingly, an acceleration is observed for polymerization without stirring. However, this phenomenon[65] can also be interpreted qualitatively in terms of eq. (81): with increasing time V_I decreases in favor of V_{II} and since $k_{tII} < k_{tI}$ an increase in v_p occurs which manifests itself as an acceleration of the reaction in the experiment. The termination constant k_t in radical polymerization is a diffusion-controlled quantity and thus roughly inversely proportional to the viscosity. Since the viscosity of phase II is considerably higher than that of phase I it follows that $k_{tII} < k_{tI}$.

9. Outlook

Investigation of polymer kinetics requires sophisticated experimental techniques. The monomer must be subjected to extremely thorough purification and above all freed from all traces of oxygen, which clearly has a profound effect on radical polymerization. Operations such as rectification and degassing generally prove inadequate; the monomer must be subjected to some degree of prepolymerization by addition of initiator. The monomer distilled from this prepolymer in high vacuum is then sufficiently pure for studies of polymer kinetics. Owing to the considerable difference in density between monomer and polymer, the decrease in reaction volume observed during reaction can be used as a measure for the conversion (dilatometry), provided a calibration between volume contraction and conversion is first established by gravimetric determinations. This greatly facilitates the plotting of conversion/time curves. However, the dilatometric method requires modification for heterogeneous polymerization[59]. It should be borne in mind when calculating the rate of polymerization that the rate of decrease in monomer concentration differs drastically (up to 56% in the case of acrylonitrile polymerization) from the polymerization rate owing to the volume change accompanying the reaction[59].

The analytical methods available for determining mean degrees of polymerization have already been mentioned. Molecular weight distributions can be ascertained by means of the ultracentrifuge, gel permeation chromatography, and fractional precipitation. Further development and refinement of the methods for characterization of polymeric products should provide access to additional information required for improvements in polymerization technology and in the quality of industrial products, and also complete our knowledge of the course of radical polymerization. In particular we still lack detailed knowledge of polymerizations proceeding in non-homogeneous manner (*e.g.* about vinyl chloride polymerization) and the effect of mixing on the mechanism of polymerization reactions occurring in disperse two-phase systems, which has only been treated qualitatively in the present progress report.

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[1] *F. A. Bovey:* The High Resolution NMR Spectroscopy of Polymers, in *A. D. Jenkins:* Progress in Polym. Sci. Pergamon Press, Oxford 1971, Vol. 3.

[2] *P. Mehnert*, unpublished.

[3] *U. Kador* and *P. Mehnert*, Makromol. Chem. *144*, 29 (1971).

[4] *K. Matsuzaki, T. Uryu, A. Ishida, T. Okhi*, and *M. Takenchi*, J. Polym. Sci. *A-1*, *5*, 2167 (1967).

[5] *G. Svegliado, G. Talamini*, and *G. Vidotto*, J. Polym. Sci. *A-1*, *5*, 2875 (1967).

[6] *G. Talamini* and *G. Vidotto*, Makromol. Chem. *100*, 48 (1967).

[7] *H. G. Elias* and *P. Göldi*, Makromol. Chem. *144*, 85 (1971).

[8] *J. Bargon, K. H. Hellwege*, and *U. Johnsen*, Makromol. Chem. *95*, 187 (1966).

[9] *F. A. Bovey, F. P. Hood, E. W. Anderson*, and *R. L. Kornegay*, J. Phys. Chem. *71*, 312 (1967).

[10] *F. A. Bovey*, J. Polym. Sci. *46*, 59 (1960).

[11] *S. Okuzawa, H. Hirai*, and *S. Makishima*, J. Polym. Sci. *A-1*, *7*, 1039 (1969).

[12] *T. G. Fox* and *H. W. Schnecko*, Polymer *3*, 575 (1962).

[13] *K. Matsuzaki, T. Uryu*, and *K. Ito*, Makromol. Chem. *126*, 292 (1969).

[14] *A. Yamada* and *M. Yanagita*, IUPAC Symp. on Macromolecular Chem., Budapest 1969. Preprints Vol. 3, p. 253.

[15] *Y. Iwakura, F. Toda, T. Ito*, and *K. Aoshima*, Makromol. Chem. *104*, 26 (1967).

[16] *J. W. L. Fordham*, J. Polym. Sci. *39*, 321 (1959).

[17] *C. E. H. Bawn, W. H. Janes*, and *A. M. North*, J. Polym. Sci. *C 4*, 427 (1964).

[18] *H. Fischer*, Kolloid-Z. Z. Polym. *206*, 131 (1965).

[19] *K. Messmer* and *P. Mehnert*, Colloid Polym. Sci. *252*, 97 (1974).

[20] *K. Messmer* and *P. Mehnert*, unpublished.

[21] *P. Mehnert*, unpublished.

[22] *D. L. Chapman, F. Briers*, and *E. Walters*, J. Chem. Soc. *1926*, 562.

[23] *H. W. Melville*, Proc. Roy. Soc. *A 163*, 151 (1937).

[24] *P. Mehnert*, unpublished.

[25] *O. L. Wheeler, E. Lavin*, and *R. N. Crozier*, J. Polym. Sci. *9*, 157 (1952).

[26] *D. J. Stein*, Makromol. Chem. 76, 170 (1964).

[27] *G. V. Schulz* and *D. J. Stein*, Makromol. Chem. *52*, 1 (1962).

[28] *F. Patat* and *J. A. Potchinkov*, Makromol. Chem. *23*, 54 (1957).

[29] *W. W. Graessley* and *H. M. Mittelhauser*, J. Polym. Sci. *A-2*, *5*, 431 (1967).

[30] *W. W. Graessley, R. D. Hartung*, and *W. C. Uy*, J. Polym. Sci. *A-2*, *7*, 1919 (1969).

[31] *P. Mehnert*, IUPAC Symp. on Macromolecular Chem., Budapest 1969. Preprints Vol. 3, p. 289.

[32] *S. Nozakura, Y. Morishima*, and *S. Murahashi*, J. Polym. Sci. *10*, 2853 (1972).

[33] *P. Mehnert*, Kolloid-Z. Z. Polym. *251*, 587 (1973).

[34] *F. Patat* and *P. Mehnert*, Monatsh. Chem. *98*, 538 (1967).

[35] *P. Mehnert*, unpublished.

[36] *B. I. Funt* and *W. Pasika*, Can. J. Chem. *38*, 1865 (1960).

[37] *P. Mehnert*, unpublished.

[38] *F. R. Mayo*, IUPAC Symp. on Macromolecular Chem., Moscow 1960. Preprints Vol. 2, p. 11.

[39] *K. Kirchner*, Makromol. Chem. *96*, 179 (1966).

[40] *K. G. Buchholz* and *K. Kirchner*, Angew. Makromol. Chem. *13*, 127 (1970).

[41] *D. J. Stein* and *H. Mosthaf*, Angew. Makromol. Chem. *2*, 39 (1968).

[42] *J. Kurze, D. J. Stein, P. Simak*, and *R. Kaiser*, Angew. Makromol. Chem. *12*, 25 (1970).

[43] *J. Wiesner* and *P. Mehnert*, Makromol. Chem. *165*, 1 (1973).

[44] *J. Wiesner* and *P. Mehnert*, Chem.-Ing.-Tech. *45*, 1269 (1973).

[45] *J. Wiesner* and *P. Mehnert*, unpublished.

[46] *J. Wiesner* and *P. Mehnert*, Kolloid-Z. Z. Polym. *251*, 607 (1973).

[47] *J. Wiesner* and *P. Mehnert*, unpublished.

[48] *H. Suess, K. Pilch*, and *H. Rudorfer*, Z. Phys. Chem. *A 179*, 361 (1937).

[49] *G. V. Schulz, A. Dinglinger*, and *E. Husemann*, Z. Phys. Chem. *B 43*, 385 (1939).

[50] *K. Kirchner*, Makromol. Chem. *128*, 150 (1969).

[51] *H. Benoit* and *C. Loucheux*, C. R. Acad. Sci. *251*, 382 (1960).

[52] *K. Marquardt* and *P. Mehnert*, Makromol. Chem. *175* (1974), in press.

[53] *C. H. Bamford* and *A. D. Jenkins*, Proc. Roy. Soc. *A 216*, 515 (1953).

[54] *C. H. Bamford, W. G. Barb, A. D. Jenkins*, and *P. F. Onyon*: The Kinetics of Vinyl Polymerization by Radical Mechanisms. Butterworths, London 1958, p. 111.

[55] *A. D. Jenkins* in *G. E. Ham*: Vinyl Polymerization. Marcel Dekker, New York 1967, Part 1, p. 377.

[56] *O. G. Lewis* and *L. M. King*, Advan. Chem. Ser. *91*, 25 (1969).

[57] *C. H. Bamford, A. D. Jenkins, M. C. R. Symons*, and *M. G. Towsend*, J. Polym. Sci. *34*, 181 (1959).

[58] *C. H. Bamford* and *A. D. Jenkins*, Proc. Roy. Soc. *A 228*, 220 (1955).

[59] *K. Marquardt* and *P. Mehnert*, Angew. Makromol. Chem. *28*, 177 (1973).

[60] *K. Marquardt* and *P. Mehnert*, Chem.-Ztg. *97*, 564 (1973).

[61] *K. Marquardt* and *P. Mehnert*, Angew. Makromol. Chem. *38*, 155 (1974).

[62] *K. Marquardt* and *P. Mehnert*, Colloid Polym. Sci., in press.

[63] *C. H. Bamford, A. D. Jenkins*, and *R. Johnston*, Trans. Faraday Soc. *58*, 1212 (1962).

[64] *K. Marquardt* and *P. Mehnert*, Naturwissenschaften *60*, 476 (1973).

[65] *K. Marquardt* and *P. Mehnert*, unpublished.

[66] *K. Noma, Y. Kawagishi*, and *M. Niwa*, Chem. High Polym. (Kobunshi Kagaku) *26*, 708 (1969).

[67] *F. Engel* and *P. Mehnert*, unpublished.

[68] *N. Grassie* and *E. Vance*, Trans. Faraday Soc. *52*, 727 (1956).

[69] *F. Engel* and *P. Mehnert*, Naturwissenschaften *58*, 96 (1971).

α-Metalated Isocyanides in Organic Synthesis

New synthetic methods (6)

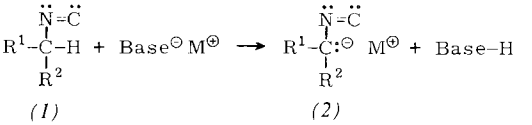
By Dieter Hoppe[*]

α-Alkali-metalated isocyanides, which can be obtained from isocyanides and bases, can be used for nucleophilic introduction of (masked) α-aminoalkyl groups. Intramolecular ring-closure may then follow if a nucleophile combines at the electron sextet of the isocyanide carbon. Treatment of α-alkali-metalated isocyanides with electrophilic agents permits rapid and efficient synthesis of, *inter alia*, 2- and 3-amino alcohols, straight-chain, branched, and β-functional α-amino acids, olefins, vinyl isocyanides, and of a large number of mainly five-, but also six- and seven-membered aza-, diaza-, oxa-aza-, and thia-aza heterocycles.

1. Introduction

Although the activating action of the cyano group[1] has been known for almost a hundred years it was only in 1968 that *Schöllkopf* and *Gerhart*[2] found that the isocyano group also makes hydrogen in the α-position acidic.

α-Metalated isocyanides *(2)* have proved to be valuable organic reagents within the few years since their discovery[3],



(1) *(2)*

and it is conceivable that in future they will become as preparatively useful as the metalated cyanides. The importance of compounds *(2)* for organic synthesis rests partly on the metalated (*i.e.* anionized) carbon atom, to which electrophilic centers can become attached, and partly on the fact that the "bivalent" isocyanide carbon[4, 5] makes subsequent heterocyclization possible. Since the isocyano group is hydrolyzed

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to an amino group under acidic conditions, the metalated isocyanides *(2)* are masked α-amino carbanions and enable α-aminoalkyl groups to be introduced nucleophilically into organic and inorganic molecules.

Alkyl isocyanides *(1)* are obtained conveniently and in high yield by dehydration of formamides[5, 4] by means of phosgene[6], phosphorus oxide trichloride[7], toluenesulfonyl chloride[8], triphenylphosphane/tetrachloromethane[9], or thionyl chloride/dimethylformamide[10] in the presence of bases. Isocyanides that are not sensitive to alkali can be prepared by the Mąkosza variant[11] of the Hofmann carbylamine reaction[12].

2. Metalation of Isocyanides

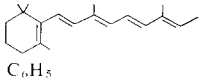
Isocyanides *(1)* that do not carry an α-hydrogen atom add Grignard reagents[13] and lithium compounds[14] to the isocyanide group, yielding metalated aldimines; the lithium derivatives have been used as acyl anion equivalents[15]. The reaction of, for example, methyl isocyanide *(3a)* (see Table 1) with *n*-butyllithium in tetrahydrofuran at −70 °C takes quite a different course—the α-hydrogen is replaced by lithium[2]. The formation of isocyanomethyllithium *(4a)*[16] was proved by reactions with carbonyl compounds[17] (cf. Section 4). It has subsequently been found that *n*-butyllithium also smoothly metalates other alkyl isocyanides such as allyl *(5)*[2], benzyl *(7)*[2], and cyclopropyl isocyanide *(9)*[18], *i.e.* those whose parent hydrocarbons are as acid as or more acid than methane on the Cram acidity scale[19].

Isocyanides containing powerfully electron-withdrawing substituents in the α-position, such as α-isocyanoalkanoic esters *(15)*, α-isocyanoalkanonitriles *(17)*, arenesulfonylmethyl isocyanides *(23)*, and α-isocyanomethanephosphonic esters *(25)*, can be completely or partially anionized by weaker bases such as potassium *tert*-butoxide, sodium hydride, sodium ethoxide, or even tertiary amines. Table 1 illustrates the main compound types[128, 129] that have been metalated so far, as well as the reaction conditions.

The cause of the acidifying action of the isocyano group is not yet quite clear, but dipole stabilization of the anion[20] is suspected[127].

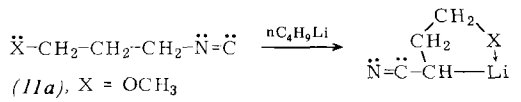
This reaction with *n*-butyllithium fails with less acidic α-alkyl-substituted isocyanides such as cyclohexyl[21] and *n*-butyl isocyanide[22], even in the presence of *N,N,N',N'*-tetramethylethylenediamine or hexamethylphosphoric triamide[23], since in these cases α-addition gains the upper hand. Metalation can, however, be forced for these isocyanides too by using strong, weakly nucleophilic bases, such as lithium 2,2,6,6-tetramethylpiperidide[24] *in situ*[25]. A special position is occupied by isocyanides *(11)*, where C-3 carries a donor group such as

Table 1. Main types of isocyanides metalated so far.

	R^1R^2CH-NC R^1	R^2	Base/Solvent/T [°C]		R^1E^2CM-NC M	Ref.
(3a)	H	H	BuLi/THF/−70	*(4a)*	Li	[2]
(3b)	CH_3	H	$LiNR_2$ [a]/THF/−70 [b]	*(4b)*	Li	[25]
(5a)	$CH_2=CH$	H	BuLi/THF/−70	*(6a)*	Li	[2]
			Cu_2O/C_6H_6/80 [b]		Cu	[31]
(5b)		H	BuLi/THF/−70	*(6b)*	Li	[28]
(7a)	C_6H_5	H	BuLi/THF/−70	*(8a)*	Li	[2]
			KOtBu/THF/−70 [b]		K	[32]
			Cu_2O/C_6H_6/80 [b]		Cu	[33]
(7b)	C_6H_5	C_6H_5	KOtBu/THF/−70	*(8b)*	K	[32]
(7c)	2-furyl	H	NaH/DMF/20 [b]	*(8c)*	Na	[22]
(9a)	$-CH_2-CH_2-$		BuLi/THF/−70	*(10a)*	Li	[18]
(11a)	$CH_3O(CH_2)_2$	H	BuLi/THF/−70	*(12a)*	Li	[30]
(11b)	$(CH_3)_2N(CH_2)_2$	H	BuLi/THF/−70	*(12b)*	Li	[26]
(13a)	C_6H_5CO	H	BuLi/THF/−70 [c]	*(14a)*	Li	[34]
(15a)	$CO_2C_2H_5$	H [d]	BuLi/THF/−70	*(16)*	Li	[35, 36]
(15b)	$CO_2tC_4H_9$	H [d]	KOtBu/THF/−70		K	[36]
(15c)	$CO_2C_2H_5$	CH_3 [d]	NaH/THF/20 [b]		Na	[37, 38]
			NaH/DMSO/20 [b]		Na	[39]
			NaOEt/EtOH/20 [b]		Na	[35, 36]
			NaCN/EtOH/20 [b]		Na	[40, 41]
			DBU [e]/THF/20 [b]			[42, 43]
			Cu_2O/C_6H_6/80 [b]		Cu	[33]
(17a)	$C\equiv N$	H	Et_3N/CH_2Cl_2/15 [b]	*(18a)*	[f]	[44]
(17b)	$C\equiv N$	$(CH_3)_2CH$	NaCN/EtOH/15 [b]	*(18b)*	Na	[44]
(19a)	$(CH_3)_3Si$	H	BuLi/THF/−70	*(20a)*	Li	[45]
(19b)	$(CH_3)_3Si$	$(CH_3)_3Si$	BuLi/THF/−70	*(20b)*	Li	[45]
(21a)	C_6H_5S	H	BuLi/THF/−70	*(22a)*	Li	[46]
(23a)	p-$CH_3-C_6H_4SO_2$	H	BuLi/THF/−70	*(24a)*	Li	[47, 48]
			KOtBu/THF/−70		K	[47, 48]
			NaH/DMSO/20 [b]		Na	[49]
			K_2CO_3/CH_3OH/65 [b]		K	[50]
			KOH/glyme/20 [b]		K	[50]
			KOH/tBuOH/20 [b]		K	[51]
(25a)	$(C_2H_5O)_2P(O)$	H	BuLi/THF/−70	*(26a)*	Li	[52, 53]
			NaCN/EtOH/20 [b]		Na	[52, 53]
			Cu_2O/C_6H_6/80 [b]		Cu	[52, 53]

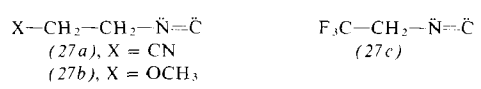
[a] $LiNR_2$ = lithium 2,2,6,6-tetramethylpiperidide or diisopropylamide.
[b] The metalated isocyanide is produced *in situ*.
[c] By lithiation of 5-phenyloxazole (cf. Section 6).
[d] *(15a)*, *(15b)*, and *(15c)* are each treated with all the reagents named.
[e] DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.
[f] See Section 5.2.

alkoxy or dialkylamino, since now the formation of a chelate has a considerable and favorable influence on lithiation[26].



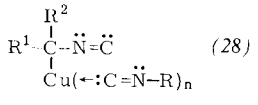
(11a), X = OCH_3
(11b), X = $N(CH_3)_2$

If the isocyanide is of type *(27)*, carrying a nucleofugal leaving group in the β-position, *e.g.* 3-isocyanopropionitrile *(27a)*[27], 2-methoxyethyl isocyanide *(27b)*[28], or 2,2,2-trifluoroethyl isocyanide *(27c)*[29], olefins are obtained when metalation is attempted.



(27a), X = CN
(27b), X = OCH_3
(27c)

The metalated isocyanides are thermolabile and decompose between −60 and 0 °C depending on their structure. If, therefore, higher temperatures are needed for their reaction it is advisable to produce them *in situ*. According to *Saegusa et al.*[31-33], benzyl *(7)* and allyl isocyanides *(5)*, as well as α-isocyanoalkanoic esters *(15)*, undergo reactions characteristic of metalated isocyanides if they are heated with carbonyl compounds or activated olefins in the presence of 1—5 mol-% of copper(I) oxide; a copper-isocyanide complex of type *(28)* with metal-carbon bonds, but of as yet incompletely elucidated structure[33], functions as a crucial intermediate.

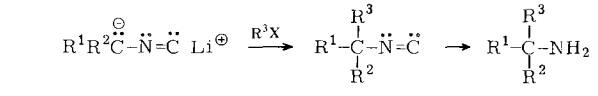


(28)

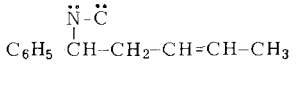
3. Alkylation of Metalated Isocyanides

3.1. Chain Extension of Amines

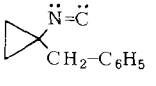
Starting from the lithiated isocyanides *(4a)*, *(6a)*, and *(8a)*, the monoalkylation products *(29)* are obtained by using alkyl bromides or iodides; *(10a)* gave *(30)*. The yields are between 30 and 90 %[54, 18]. Since isocyanides are obtained from amines and are reconverted into amines by acid hydrolysis[55], this sequence constitutes a method for α-alkylating primary amines. Homoallyl- and tertiary cyclopropylamines that are otherwise difficult to prepare, can be synthesized conveniently by this method, *e.g. via (29a)* or *(30a)*.



(4a), *(6a)*, *(8a)*, *(10a)* *(29)*, *(30)*



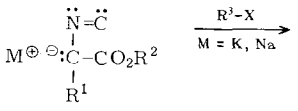
(29a), 89% [54]



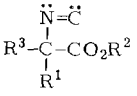
(30a), 76% [18]

3.2. Alkylation of Metalated α-Isocyanoalkanoic Esters; Synthesis of Amino Acids

Alkylation of α-metalated α-isocyanoalkanoic esters *(16)* is of interest because its overall effect is the production of longer-chain or α-branched amino acids[39]. For this purpose an alkyl halide R^3X was brought into reaction with a solution of the potassium compound *(16)*, M = K, in tetrahydrofuran, prepared from *(15)* and potassium *tert*-butoxide, or of the sodium compound *(16)*, M = Na, produced *in situ* by sodium hydride in dimethyl sulfoxide/ether. Alkylation of ethyl α-isocyanopropionate *(15c)* is unambiguous, leading to 2-isocyano-2-methylalkanoic esters *(33)*.

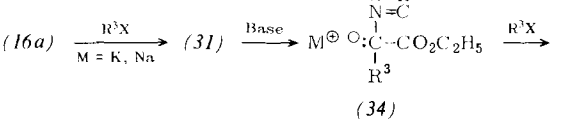


(16a), R^1 = H, R^2 = C_2H_5
(16b), R^1 = H, R^2 = tC_4H_9
(16c), R^1 = CH_3, R^2 = C_2H_5

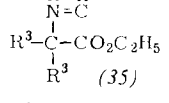


(31), R^1 = H, R^2 = C_2H_5, R^3 = Alkyl
(32a), R^1 = H, R^2 = tC_4H_9, R^3 = $(CH_3)_2CH$: 60% [39]
(33a), R^1 = CH_3, R^2 = C_2H_5, R^3 = $CH_2C_6H_5$: 79% [39]

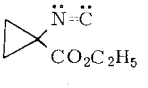
From ethyl isocyanoacetate *(15a)*, however, mainly the dialkylation product *(35)* is isolated, along with *(31)* and unchanged starting material; this accords with experience gained with other CH-acidic compounds[56]. 1,2-Dibromoethane and 2-chloroethyl toluenesulfonate give respectively 58 and 30 % of ethyl 1-isocyano-1-cyclopropanecarboxylate *(36a)*[39, 76]. The cycloalkylation cannot be applied to secondary or tertiary dihaloalkanes—these react mainly with elimination—so that ring-substituted esters of this type are better prepared by methylenation of 2-isocyanoacrylic esters *(74)* (cf. Section 4.3.1).



(34)



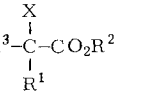
(35a), R^3 = nC_4H_9 : 71% [39]



(36a), 58% [39, 76]

Monoalkylation to give *(32)* is, however, successful with *tert*-butyl isocyanoacetate *(15b)*, since here the bulky ester group prevents attack by a second alkyl halide molecule[39].

2-Isocyanoalkanoic esters of types *(31)*—*(33)*, *(35)*, and *(36)* are convertible by ethereal hydrogen chloride at −10 to 0 °C into *N*-formylamino acid esters *(37)*, by ethanolic hydrogen chloride at room temperature into amino acid ester hydrochlorides *(38)*, and by hot aqueous hydrochloric acid into the amino acids themselves *(39)*[39].

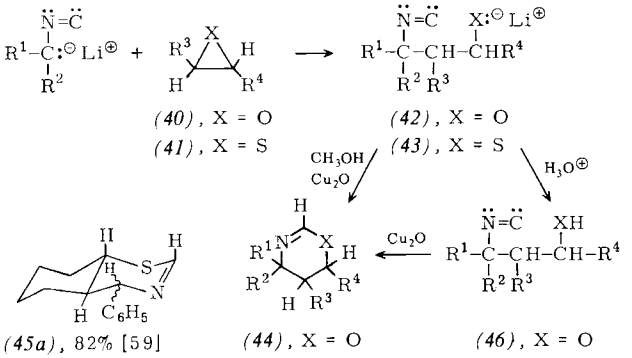


(37), X = NHCHO, R^2 = Alkyl
(38), X = $NH_3^{\oplus}Cl^{\ominus}$, R^2 = Alkyl
(39), X = NH_2, R^2 = H

Attempts at asymmetrically induced synthesis of L-(−)-α-methyl-3,4-dihydroxyphenylalanine (α-methyldopa) by alkylation of (−)-menthyl or (+)-bornyl α-isocyanopropionate gave optical yields of around 10%[57]. *van Leusen et al.*[49] have reported base-induced alkylation of arenesulfonylmethyl isocyanides *(23)*; here too monoalkylation encountered difficulties.

3.3. Alkylation by Epoxides, Episulfides, and Oxetanes

Metalated isocyanides attack epoxides *(40)* at −70 to 0°C at the less substituted carbon atom. The lithium salts *(42)* can be either protonated to give 3-isocyano alcohols *(46)* or cyclized[30,59] to 5,6-dihydro-4*H*-1,3-oxazines *(44)* by warming with methanol or, better, copper(I) oxide[58].



(40), X = O; *(41)*, X = S

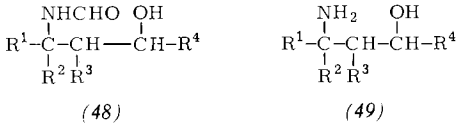
(42), X = O; *(43)*, X = S

CH_3OH, Cu_2O; $H_3O^{\oplus}$; Cu_2O

(45a), 82% [59]

(44), X = O; *(45)*, X = S

(46), X = O; *(47)*, X = S



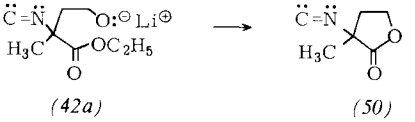
(48) *(49)*

The isocyanides *(46)* can be converted quantitatively into (3-hydroxyalkyl)formamides *(48)* or 3-amino alcohols *(49)*[30].

3-Isocyanoalkanethiols *(47)* can be obtained from the lithiated isocyanides *(4)*, *(6)*, and *(8)* and episulfides *(41)*, these products being partially converted into 5,6-dihydro-4*H*-1,3-thiazines *(45)* even at room temperature[60,59].

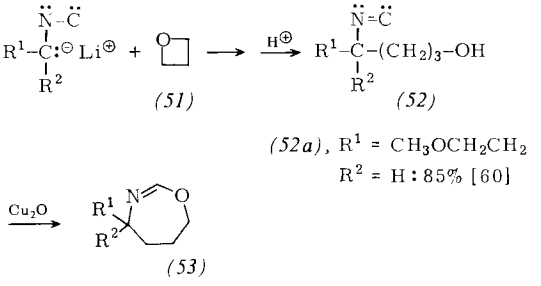
Episulfides that are derived from conjugated olefins do not undergo nucleophilic ring opening of the thiirane ring, because in their case desulfuration occurs with the formation of olefin[61,59].

The (less nucleophilic) α-metalated ethyl isocyanoacetate *(16a)* attacks neither epoxides nor episulfides. Here, as in an inert medium, "self-condensation" (cf. Section 6.1) is dominant. However, lithiated ethyl α-isocyanopropionate *(16c)* with ethylene oxide affords a 51% yield of 2-isocyanobutyrolactone *(50)*, whose formation can be explained by lactonization of the adduct *(42a)*. When warmed with an excess of ethoxide, the lactone *(50)* rearranges (*via* the open-chain ester) to the dihydrooxazine *(44)*[30].



(42a) *(50)*

Oxetanes *(51)* react only above 0°C with metalated isocyanides[60]. For that reason only the less thermolabile compounds with sufficient nucleophilicity, *e.g.* lithiated benzyl *(8a)* or 3-methoxypropyl isocyanide *(12a)*, afford the 4-isocyano alcohols *(52)* in satisfactory yield. Their cyclization to 4,5,6,7-tetrahydro-1,3-oxazepines *(53)* with catalysis by copper also occurs in only moderate yield, since intermolecular polyaddition predominates[60].



(51) *(52)*

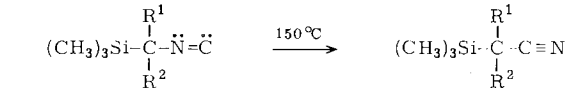
(52a), $R^1 = CH_3OCH_2CH_2$, $R^2 = H$: 85% [60]

Cu_2O

(53)

3.4. Silylation

Lithiomethyl isocyanide *(4a)* reacts with trimethylchlorosilane even at −78°C, yielding (trimethylsilyl)methyl isocyanide *(19a)*[45]; stepwise lithiation and renewed silylation afford bis- and tris(trimethylsilyl)methyl isocyanide [*(19b)* and *(19c)*].



(19a), $R^1 = R^2 = H$

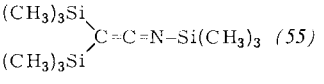
(19b), $R^1 = (CH_3)_3Si$, $R^2 = H$

(19c), $R^1 = R^2 = (CH_3)_3Si$

150°C

(54a), $R^1 = R^2 = H$

(54b), $R^1 = (CH_3)_3Si$, $R^2 = H$



(55)

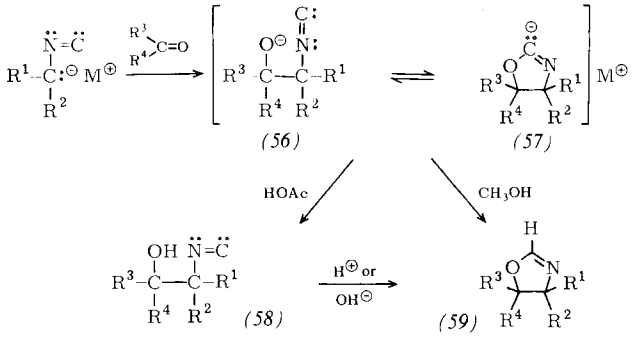
When warmed to 150°C, *(19a)* rearranges to (trimethylsilyl)-acetonitrile *(54a)*, whereas *(19c)* isomerizes to tris(trimethylsilyl)ketene imine *(55)*. Thermolysis of bis(trimethylsilyl)methyl isocyanide *(19b)* affords a mixture of *(54a)*, *(54b)*, and *(55)*.

4. Reaction with Aldehydes and Ketones in an Aprotic Medium

4.1. Synthesis of 2-Oxazolines; 2-Isocyano Alcohols and 2-Amino Alcohols

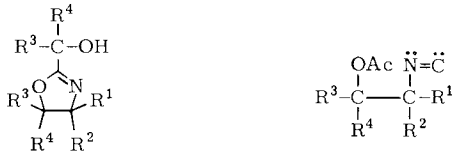
Lithioalkyl isocyanides of types *(4)*, *(6)*, *(8)*, *(10)*, *(12)*, and *(22)* (prepared by means of *n*-butyllithium in tetrahydrofuran at −70°C) add to aldehydes and ketones at −70°C, yielding 2-isocyano alkoxides *(56)* which exist in mobile equilibrium[62,92] with the 2-oxazolinyl anions *(57)*. Protonation with water at room temperature[17] or, better, with methanol at −70°C[32] affords 2-oxazolines *(59)* in 60—90% yield. However, neutralization by glacial acetic acid at *ca.* −70°C and working up under mild conditions permit isolation of the 2-isocyano alcohols *(58)*[26], which equally cyclize to *(59)* on treatment with (anhydrous) acid or base. If $R^1 \neq R^2$ and

$R^3 \neq R^4$, diastereoisomeric mixtures are obtained, *e.g. (59a)* in the *cis/trans* ratio 1 : 3[32, 63]. 2-(Hydroxyalkyl)-2-oxazolines *(60)* are found as by-products, particularly when aromatic aldehydes or ketones are used. Control experiments have shown[32] that these are formed from the oxazolinyl anion *(57)* and the carbonyl compound: for instance, if 4,5-diphenyl-2-oxazoline is metalated with *n*-butyllithium at −70 °C to the 2-lithio derivative (proved by deuteriolysis) and benzaldehyde is added, then 2-(α-hydroxybenzyl)-2-oxazoline *(60b)* can be isolated in 60% yield[32]. However, the anion *(56)* can be trapped almost quantitatively by acyl chlorides as the 2-isocyanoalkyl ester of a carboxylic acid *(61)*[26, 32].



(58a), $R^1 = R^2 = H$, $R^3 = CH_3$, $R^4 = C_6H_5$: 75% [26]

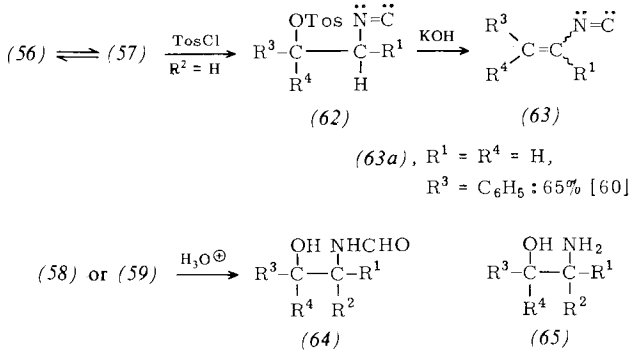
(59a), $R^1 = R^3 = C_6H_5$, $R^2 = R^4 = CH_3$: 87% [32]



(60a), $R^1 = R^2 = R^3 = R^4 = C_6H_5$: 95% [17]

(60b), $R^1 = R^3 = H$, $R^2 = R^4 = C_6H_5$

(61)



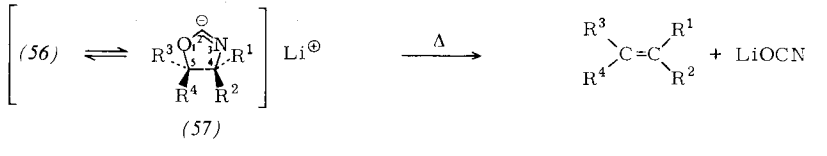
(63a), $R^1 = R^4 = H$, $R^3 = C_6H_5$: 65% [60]

mina[27, 32], whereas 2-amino alcohols *(65)* are formed with the use of aqueous or alcoholic hydrochloric acid[66]. This sequence [with *(4)*], combined with a Tiffeneau-Demyanov rearrangement, has been recommended[66] for the homologation of cyclic ketones. 2-Oxazolines *(59)* are formed also on heating sufficiently acidic isocyanides, *e.g.* types *(5)*, *(7)*, and *(15)*, with an excess of the carbonyl compound in the presence of 1—5 mol-% of copper(I) oxide[31, 33]; the course of the reaction is not yet clear in detail.

4.2. Carbonyl Olefination by Metalated Isocyanides

If the adduct formed from, for instance, α-isocyanobenzhydryllithium and benzaldehyde, *i.e. (56a)*⇌*(57a)*, is warmed to room temperature, the product isolated is not the oxazoline *(59)* but, together with lithium cyanate, a 74% yield of 1,1,2-triphenylethylene *(66a)*, which is the result of a carbonyl olefination[2].

This fragmentation can be formulated as a [4+2]-cycloreversion[67, 68] of a (hetero)cyclopentenyl anion, for which theory requires suprafacial removal of the cyanate ion in a concerted thermal reaction. Experimentally it could be shown that the fragmentation occurs stereospecifically, since *cis*-stilbene



(57a), $R^1 = R^2 = R^3 = C_6H_5$, $R^4 = H$

(57b), $R^1 = R^3 = C_6H_5$, $R^2 = R^4 = H$

(57c), $R^1 = R^2 = C_6H_5$, $R^3 = R^4 = CH_3$

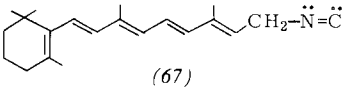
(57d), $R^1 = CH{=}CH_2$, $R^2 = R^3 = H$, $R^4 = C_6H_5$

(66a), $R^1 = R^2 = R^3 = C_6H_5$, $R^4 = H$

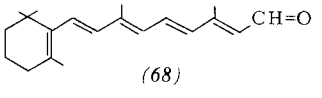
(66b), $R^1 = R^3 = C_6H_5$, $R^2 = R^4 = H$

(66d), $R^1 = CH{=}CH_2$, $R^2 = R^3 = H$, $R^4 = C_6H_5$

(66e), 60% [18]



(67)



(68)

An "*Eintopf*"[*] synthesis[60] of vinyl isocyanides *(63)*, which are difficultly accessible by conventional routes[10, 64, 65], is provided by treatment of *(56)*⇌*(57)* with *p*-toluenesulfonyl chloride, to yield *(62)*, followed by elimination of toluenesulfonic acid.

2-(Hydroxyalkyl)formamides *(64)* are obtained from either the oxazolines *(59)* or the isocyano alcohols *(58)* by mild hydrolysis, *e.g.* with methanol in the presence of basic alu-

(66b) was obtained on decomposition of *cis*-2-lithio-4,5-diphenyl-2-oxazoline *(57b)*[69]. On the basis of very different reaction rates of oxazolinyl anions *(57)* that are inversely substituted on C-4 and C-5, it is presumed that fission of the C^4—N and the C^5—O bond will not have progressed equally in the transition stage. Carbonyl olefination occurs only when the oxazolinyl anion *(57)* carries one or more groups at C-4 and/or C-5 such as phenyl or vinyl that are capable of resonance. Presumably formation of the (energy-poor) lithium cyanate plays no part as a driving force in

[*] From the German term for a stew, being prepared in a single vessel.

this transition state, perhaps because the cyanate ion must be split off from the olefin as an angled particle and can pass into the energetically favorable sp-hybrid only after the bond has broken.

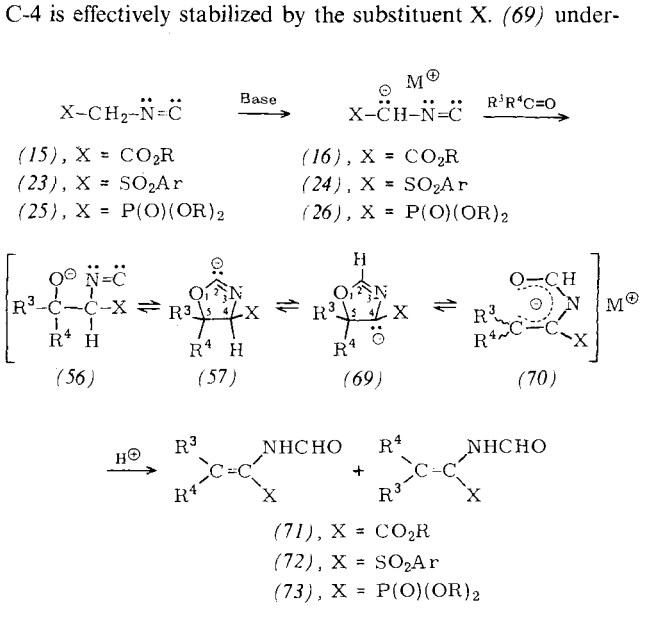
Accumulation of substituents on the oxazoline ring, as in *(57c)*, also hinders carbonyl olefination. Two factors seem to be responsible for this: First, *(57)* must occur in sufficiently high proportion in the equilibrium *(56)*⇌*(57)*; increasing substitution will worsen the position of the equilibrium since vicinal substituents on a five-membered ring are almost eclipsed. As second factor, the substituents hinder the optimal planar arrangement of neighboring sp^2-centers; in these cases there is a predominance of side reactions such as reversion of *(56)* to the starting compounds and their irreversible subsequent reactions[69].

Even though the isocyanide olefination thus cannot compete in its range of application with the universal Wittig reaction[70], it nevertheless deserves attention in some cases: for example, isomer-free (*E*)-1-phenyl-1,3-butadiene *(66d)* is formed from lithioallyl isocyanide and benzaldehyde[28, 2]; all-*trans*-retinyl isocyanide *(67)* and all-*trans*-retinal *(68)* afford 60% of equally isomer-free (all-*trans*-)β-carotene[28].

Carbonyl olefination by metalated isocyanides can complement the Wittig reaction in cases where the latter fails owing to increased stabilization of the phosphonium ylide; for instance, α-lithiobenzhydryl isocyanide and benzaldehyde afford *(66a)*, whereas triphenylphosphonium diphenylmethylide does not react with aldehydes[70].

4.3. Metalated Isocyanides of Types *(16)*, *(24)*, and *(26)*; Formylaminomethylenations

Surprisingly, the reactions of metalated isocyanides *(16)*, *(24)*, and *(26)*[11, 29] with aldehydes and ketones occur in aprotic media. In these reagents the carbon atom attached to the metal carries, besides one hydrogen atom, a strongly acidifying substituent (CO_2R, SO_2Ar, or $P(O)(OR)_2$). It is true that these add also to the carbonyl compounds to yield the adducts *(56)*⇌*(57)* (cf. Section 4.1), but now *(57)* tautomerizes to the oxazolinyl anion *(69)* because the negative charge on C-4 is effectively stabilized by the substituent X. *(69)* undergoes rapid ring fission[71], usually occurring between −70 and 0 °C and leading to the "pentadienyl anion" *(70)* which can be obtained by protonation in the form of the isomeric alkenylformamide *(71)* or *(72)*. In these reactions the end effect is that an oxo-oxygen atom is replaced by a formylaminomethylene group, and therefore the designation "formylaminomethylenation" has been proposed[3].



For comparison, the anions *(69)* were prepared from *(59)* by means of, for example, potassium *tert*-butoxide. Experimentally ring opening to give *(70)* was observed, which proves the reaction course postulated above[36, 53]. Two directions of rotation are possible for the change *(69)*→*(70)*. It has also been found that even when the substituents R^3 and R^4 have widely different space-filling capacity the two isomers of *(71)* and *(72)* are formed in comparable amounts[36]. Surprisingly, similar high activation barriers thus have to be overcome for both directions of rotation (cf. Fig. 1).

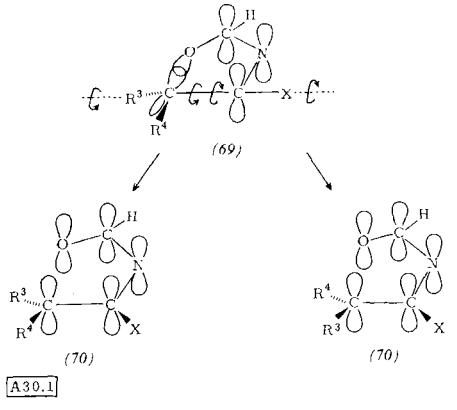
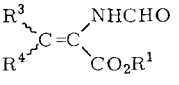


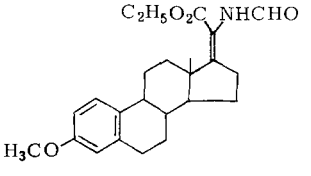
Fig. 1. Stereochemistry of formylaminomethylenation.

4.3.1. α-(Formylamino)acrylic Esters; Amino Acid Syntheses

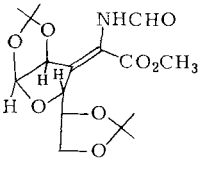
α-(Formylamino)acrylic esters *(71)* are conveniently obtained by the formylaminomethylenation of aldehydes and ketones with potassium or sodium compounds *(16)*[35, 36, 72]. Two standard procedures are to be recommended. Ethyl isocyanoacetate *(15a)* is metalated by potassium *tert*-butoxide in tetrahydrofuran at −70 °C and after addition of the carbonyl compound and warming to room temperature the mixture is worked up as usual[35, 36]. Estrone methyl ether, with its sterically hindered carbonyl group, must however be boiled in THF under reflux[73]; *(71c)* is formed. If sodium hydride



(71a), $R^1 = C_2H_5$, $R^3 = R^4 = CH_3$: 76% [35, 36]
(71b), $R^1 = tC_4H_9$, $R^3 = CH_3$, $R^4 = C_6H_5$: 85% [72, 36]



(71c), 80% [73]



(71d), 70% [80]

(in THF) is used as base, then *(16a)* is produced *in situ*, as *(15a)* and the carbonyl compound are dropped in simultaneously at 20°C[36,38].

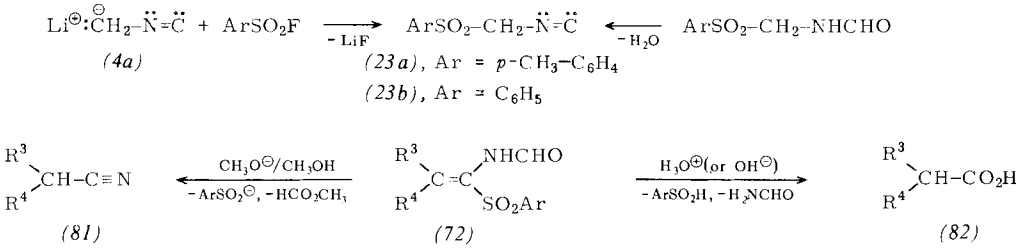
Formylaminomethylenation has some advantages over the classical Erlenmeyer azlactone process[74]: it usually occurs under mild conditions and gives good yields, even with carbonyl compounds that otherwise react with difficulty. Furthermore, it affords not the acids but esters, which are more useful for further reactions. The ready and selective removability of the formyl group constitutes yet another advantage[55].

Scheme 1 below shows some of the variations that are possible with the esters *(71)*. Hydrogenation, which can also be effected asymmetrically[75], gives *N*-formylamino esters *(77)*. Cysteine derivatives *(75)* are accessible by the addition of thiols[37,38]; *S*-benzyl-*N*-formylpenicillamine *(75a)*, for instance, can thus be obtained from ethyl isocyanoacetate in an "*Eintopf*" process. Conversion into α-isocyanoacrylic esters *(74)* offers further preparative possibilities[76]: with dimethylsulfoxonium methylide esters *(74)* afford 1-isocyano-1-cyclopropanecarboxylic esters *(79)*[76], which are precursors of 1-aminocyclopropanecarboxylic acids, a procedure that complements their synthesis by cycloalkylation (cf. Section 3.2). Grignard reagents add to *(74)*, yielding *(80)*[77], which permits the synthesis of β-tertiary amino acids. Finally, base-catalyzed reaction with hydrogen sulfide leads almost quantitatively to 5-substituted 2-thiazoline-4-carboxylic esters *(78)*[78], which can also be obtained by direct sulfuration of the acrylic esters *(71)* by tetraphosphorus decasulfide[78]. Thiazolines of type *(78)* have found application in the synthesis of modified penicillins[79].

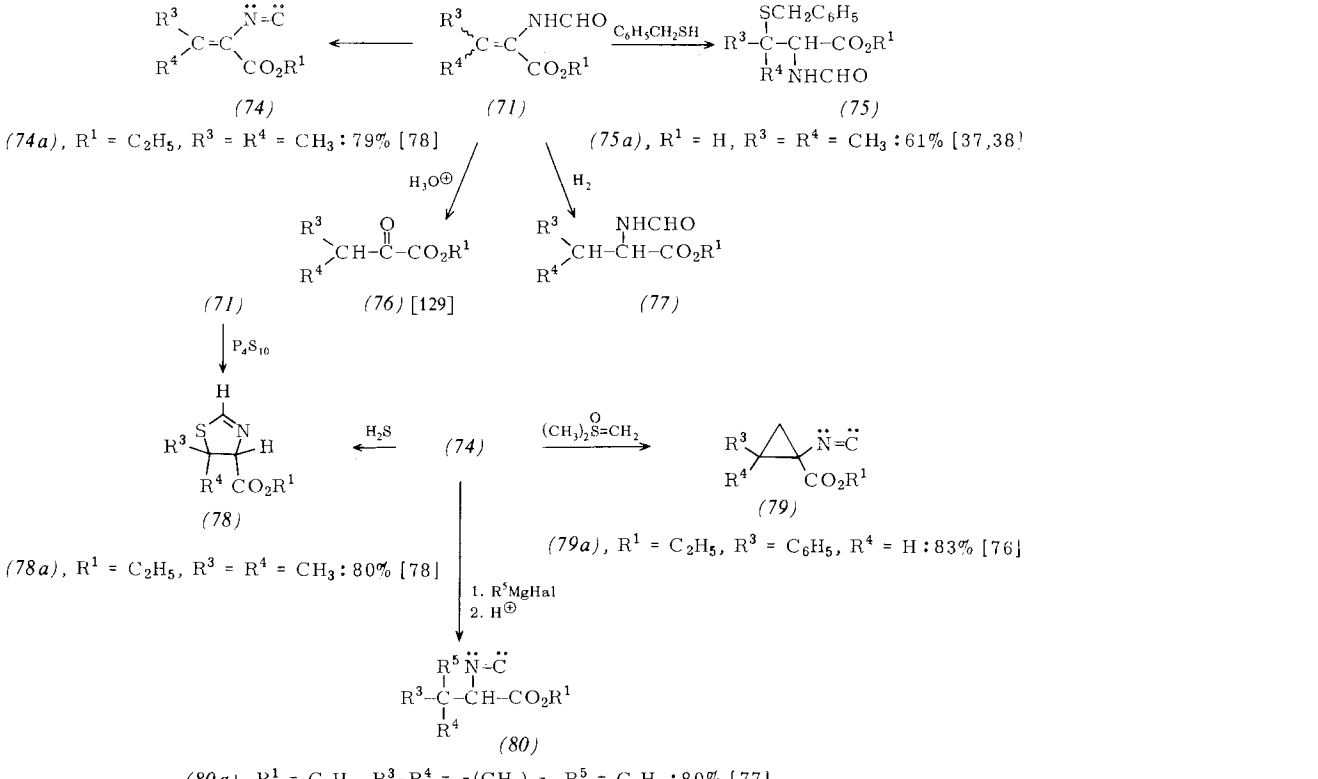
4.3.2. *N*-(1-Arenesulfonyl-1-alkenyl)formamides; Conversion of an Oxo Group into a Cyano or Carboxy Group

Arenesulfonylmethyl isocyanides *(23)* can be obtained from *(4a)* and arenesulfonyl fluorides[48,49] or, better, the formamides[48,49,82] (prepared by aminomethylation of arenesulfinic acids with hydroxymethylformamide[81]). Their potassium salts *(24)* react with aldehydes and ketones at −10°C in tetrahydrofuran, yielding *N*-(1-arenesulfonyl-1-alkenyl) formamides *(72)*.

These formamides can be converted almost quantitatively into carboxylic acids *(82)* by aqueous acid or base[47,48] or into nitriles *(81)* by sodium methoxide[83,84]. This reaction sequence thus allows conversion of a carbonyl compound into the next higher carboxylic acid or nitrile.



(81a), R^3–R^4 = -$(CH_2)_5$-: 85% [83] *(72a)*, R^3 = R^4 = H, Ar = *p*-CH_3-C_6H_4: 81% [95] *(82a)*, R^3 = $C(CH_3)_3$, R^4 = H: 90% [48]



(74a), R^1 = C_2H_5, R^3 = R^4 = CH_3: 79% [78] *(75a)*, R^1 = H, R^3 = R^4 = CH_3: 61% [37,38]

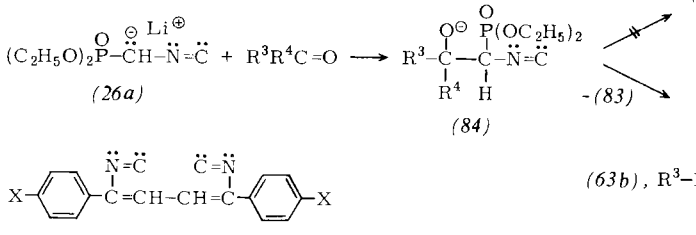
(78a), R^1 = C_2H_5, R^3 = R^4 = CH_3: 80% [78] *(79a)*, R^1 = C_2H_5, R^3 = C_6H_5, R^4 = H: 83% [76]

(80a), R^1 = C_2H_5, R^3-R^4 = -$(CH_2)_5$-, R^5 = C_2H_5: 80% [77]

Scheme 1

4.3.3. Vinyl Isocyanides and Dialkyl 1-(Formylamino)-1-alkenephosphonates

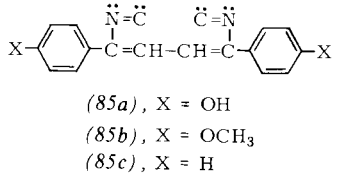
The lithium compound *(26a)* can be prepared from diethyl isocyanomethanephosphonate *(25a)* by *n*-butyllithium[52]; its reaction with carbonyl compounds does not involve formylaminomethylenation but affords *ca.* 80% of vinyl isocyanides *(63)*[52,53], which is the result of Wittig olefination. Apparently the reversible cyclization of *(84)* to the oxazolinyl anions *(57)* and *(69)*, which could then lead to formylaminomethylenation, is a non-occurring variant: decomposition of the adduct *(84)* into lithium diethyl phosphate *(83)* and vinyl isocyanide *(63)* determines the course of the reaction.



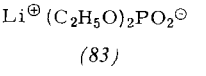
(26a) *(84)* *(63)*

(63b), R^3–R^4 = -$(CH_2)_5$- : 84% [53]

(57) ⇄ *(69)* → *(73)*

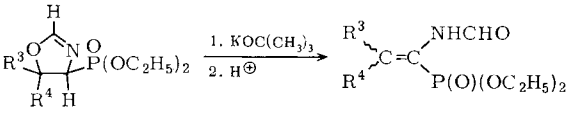


(85a), X = OH
(85b), X = OCH_3
(85c), X = H



(83)

As a preliminary study for the synthesis of isoxanthocillin *(85a)* the diisocyanide *(85c)* was synthesized from diethyl α-isocyanophenylmethanephosphonate and glyoxal[53].

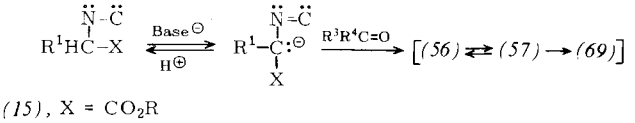


(90) *(73)*

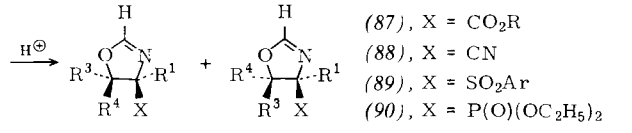
1-(Formylamino)-1-alkenephosphonic esters *(73)* can, however, be obtained by base-induced ring opening of the oxazoline-4-phosphonic esters *(90)* (cf. Section 5.3)[52,53]

5. Base-catalyzed Reaction of Relatively Acidic Isocyanides with Aldehydes and Ketones in Protic Media; Synthesis of Oxazolines

In order that the isocyanides *(15)*, *(17)*, *(23)*, and *(25)* with especially marked CH-acidity may afford oxazolines, *(87)*, *(88)*, *(89)*, and *(90)* respectively, all with R^1=H, on reacting with carbonyl compounds the reaction medium must be weakly basic and protic; otherwise competing and/or subsequent reactions predominate (cf. Section 4.3).



(15), X = CO_2R
(17), X = C≡N
(23), X = SO_2Ar
(25), X = $P(O)(OC_2H_5)_2$

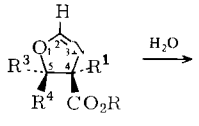


(87), X = CO_2R
(88), X = CN
(89), X = SO_2Ar
(90), X = $P(O)(OC_2H_5)_2$

Ethanol has proved useful as the solvent, and sodium cyanide (5—10 mol-%) as the catalyst[40,41] which provides a weakly basic medium as a result of its partial alcoholysis; sodium ethoxide (*ca.* 5 mol-%) in ethanol has also been recommended[35,36]. Triethylamine in dichloromethane[44] proved optimal for α-isocyanoalkanonitriles *(17)*. *Saegusa*'s copper oxide method[31,33] seems to be generally applicable. Whereas diastereoisomeric 2-oxazolines ($R^3 \neq R^4$) having a hydrogen atom on C-4 equilibrate in the basic medium by way of the anion *(69)* to give the thermodynamically favored (*trans*)-isomers, the copper-catalyzed reaction gives mixed diastereoisomers also in these cases[33].

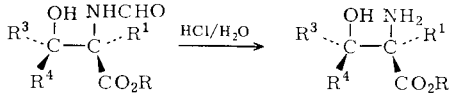
5.1. Alkyl 2-Oxazoline-4-carboxylates and Serine

50—90% yields of ethyl 2-oxazoline-4-carboxylates *(87)* can be obtained from ethyl isocyanoacetate *(15a)* and carbonyl compounds by the "cyanide process"[40,41], the 5-monosubstituted esters R^1=R^3=H) being isolated to more than 95%



(87) [85]

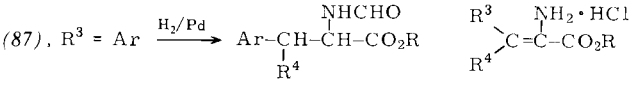
(87a), R^1 = R^4 = H, R^3 = CH_3
R = C_2H_5



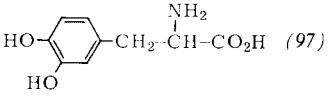
(91), R = Alkyl
(92), R^3 = Ar, R = H

(93), R = CH_3, R^1 = Alkyl, R^3, R^4 = Ar, H

(94), R = H



(95), R = Alkyl *(96)*



(97)

as the *trans*-forms. α-Isocyanoalkanoic esters such as α-isocyanopropionic esters *(15c)*, R^1=CH_3, similarly afford 4-alkyl-2-oxazoline-4-carboxylic esters.

As imidic esters, the oxazolines *(87)*[86] can be hydrolyzed to *N*-formylserine esters *(91)*[41,87]. In neutral to weakly basic medium the hydrolysis occurs with retention of the configuration at C-4 and C-5. Using 6 N hydrochloric acid (*ca.* 100 °C; 1—2 h) one thus obtains the serine derivatives *(94)*; ethyl *trans*-5-methyl-2-oxazoline-4-carboxylate *(87a)*, for example, yields exclusively D,L-threonine. *Matsumoto et al.*[88] prepared ring-methoxylated, α-alkylated phenylserine methyl esters *(93)* by treating methyl α-isocyanoalkanoates *(15)*, R^1 = alkyl, with aromatic aldehydes (sodium hydride in tetrahydrofuran, 20 °C) and hydrolyzing the oxazoline *(87)* *in situ* with methanolic hydrochloric acid (2 h, 50 °C). The proportion of *threo*-*(93)* increases with increasing bulk of the alkyl group.

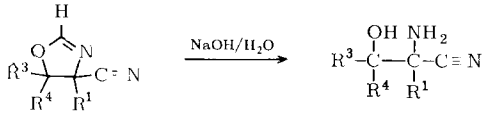
Difficulty is experienced in acid deformylation of β-branched and β-alkoxyphenyl-substituted *N*-formylserine esters *(91)*, $R^1 = H$[89], which are readily dehydrated to α-aminoacrylic ester hydrochlorides *(96)*. *Damico et al.*[90] used this effect for a synthesis of D,L-dopa *(97)* from methyl isocyanoacetate and 3,4-dibenzyloxybenzaldehyde; hydrogenation of the hydrochloride of type *(96)* simultaneously removed the benzyl groups. Hydrogenolysis of 5-aryl-substituted oxazolines *(87)*[91] provides a route to *N*-formylphenylalanine esters *(95)*.

(−)-α-Methylserine *(94)*, $R^1 = CH_3$, $R = R^3 = R^4 = H$, is obtained by the reaction of (−)-menthyl α-isocyanopropionate with formaldehyde and subsequent hydrolysis, although the optical yield in this asymmetric synthesis amounts to only 20 %[93].

Treatment of isocyanoacetic esters *(15a)* with aromatic aldehydes or ketones and an excess of sodium hydroxide in tetrahydrofuran[35,36] affords *N*-formyl-β-arylserines *(92)*; the active base is probably not the alkali metal hydroxide but the alkoxide formed by hydrolysis (cf. Section 8.1).

5.2. 2-Oxazoline-4-carbonitriles

1-Isocyanoalkyl cyanides *(17)*[44] are prepared by dehydration of *N*-(1-cyano-1-alkyl)formamides[94] and react with aldehydes or ketones in dichloromethane in the presence of triethylamine even at room temperature to yield 2-oxazoline-4-carbonitriles *(88)*[44], the hydrolysis of which by aqueous sodium hydroxide at 20 °C affords 2-amino-3-hydroxyalkanonitriles *(98)*[44].

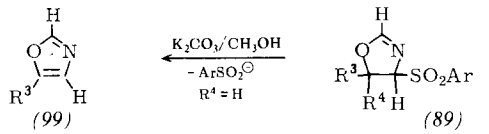


(88) *(98)*

(88a), $R^1 = (CH_3)_2CH$, $R^3 = H$, $R^4 = CH{=}CH{-}C_6H_5$: 93% [44]

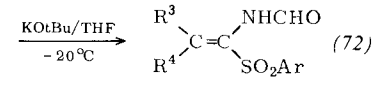
5.3. 4-Arenesulfonyl-2-oxazolines and Dialkyl 2-Oxazoline-4-phosphonates

p-Toluenesulfonylmethyl *(23a)* and benzenesulfonylmethyl isocyanide react with carbonyl compounds by the "cyanide process"[48] (at 15—30 °C) or in methanolic potassium carbonate (at 20 °C)[50] to give 60—95 % yields of 4-arenesulfonyl-2-oxazolines *(89)*.



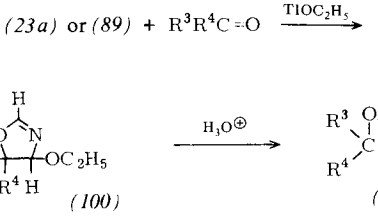
(99) *(89)*

(99a), $R^3 = C_6H_5$: 94% [50] *(89a)*, $R^3 = C_6H_5$, $R^4 = H$, $Ar = p\text{-}CH_3\text{-}C_6H_4$: 94% [48]



(72)

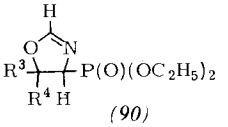
Although these products *(89)* undergo ring opening to vinylformamides *(72)* in an aprotic medium (*ca.* −20 °C) in the presence of strong bases (cf. Section 4.3.2), yet if there is a proton in position 5 they eliminate toluenesulfinic acid almost quantitatively, giving 5-monosubstituted oxazoles *(99)*, when warmed with a base in methanol[50]. When thallium(I) ethoxide is used the sulfonyl group is replaced by an ethoxy group[96]; the 4-ethoxy-2-oxazolines *(100)* thus obtained can be converted into the monomeric 2-hydroxy aldehydes *(101)*[97].



(100) *(101)*

(100a), R^3–R^4 =  : 62% [97]

(101a), R^3–R^4 =  : 78% [98]



(90)

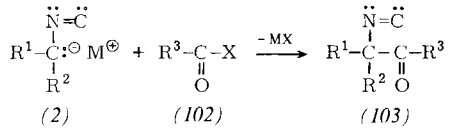
(90a), $R^3 = C_6H_5$, $R^4 = H$: 71% [53]

Diethyl 2-oxazoline-4-phosphonates *(90)* are obtained from diethyl isocyanomethanephosphonate and aldehydes or ketones in 50—70 % yield by either the "cyanide" or the "copper oxide" process[53].

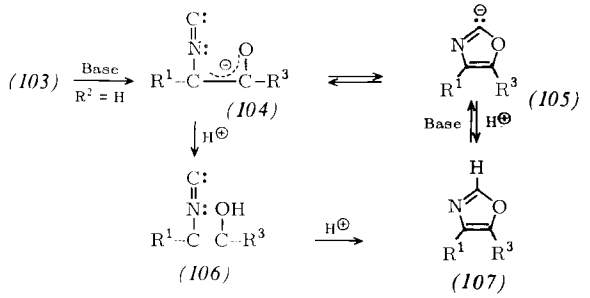
6. Reaction with Acylating Agents

Acylation of metalated isocyanides gives α-isocyano ketones *(103)* [and *(108)*] which undergo various subsequent reactions depending on the nature of the substituents R^1, R^2, and R^3. Suitable acylating agents *(102)* are acid chlorides, anhydrides, esters, and dimethylamides, and especially ethyl chloroformate and diethyl carbonate.

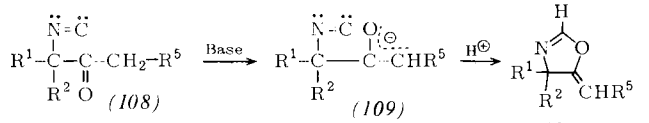
If R^1 or R^2 is hydrogen, the relatively acidic isocyano ketone *(103)* is deprotonated by a base, *e.g.* by unchanged metalated isocyanide. The enolate *(104)* is either further acylated (cf. Section 6.2) or is cyclized to the oxazolyl anion *(105)*. Protonation leads to the oxazole *(107)*, perhaps by way of *(106)*[98]. That the anions *(104)* and *(105)* exist in mobile equilibrium can be shown by metalating 5-phenyloxazole *(107)*, $R^1 = H$, $R^3 = C_6H_5$, with *n*-butyllithium[34]: the anion *(105)* was



(2) (102) (103)



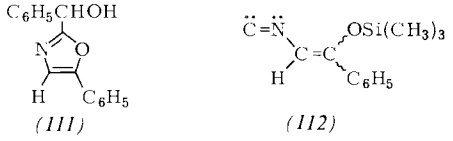
(104) (105) (106) (107)



(108) (109) (110)

R^1, $R^2 \neq H$

(110a), $R^1 = CO_2C_2H_5$, $R^2 = R^5 = CH_3$: 68% [99]

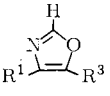


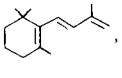
(111) (112)

trapped [as oxazole (111)] by benzaldehyde, and the anion (104) [as the enol ether (112)] by trimethylchlorosilane[34]. If the α-position is blocked by alkyl or aryl groups as in (108) and R^3 is capable of enolization, then the 5-alkylidene-2-oxazoline (110) can be formed by way of the enolate (109)[99].

6.1. Syntheses of Oxazoles

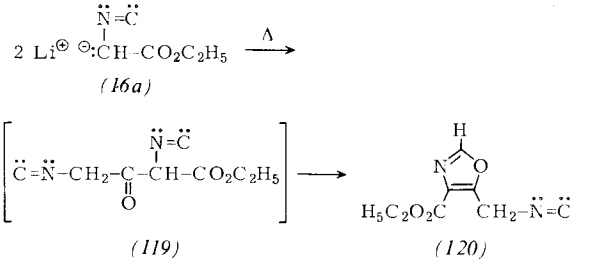
In oxazole synthesis it should be noted that additional metalated isocyanide (2) is often consumed (cf. Section 6); in the reaction with acid chlorides or anhydrides (102) double the stoichiometric amount of metalated isocyanide is used and the excess of isocyanide is either distilled off during working-up or is destroyed by aqueous acid. The utilization of (2) is improved by acylation with esters of *N,N*-dialkylamides (102), for the liberated alkoxide or dialkylamide ($X^{\ominus} = RO^{\ominus}$ or $R_2N^{\ominus}$, respectively) takes over the deprotonation of the isocyano ketone (103)[100]. According to *Matsumoto et al.*[42,43], in the presence of an excess of tertiary amine or sodium hydride the isocyanoacetic esters (15) condense with aroyl chlorides also in the proportion of 1 : 1, yielding 5-aryloxazole-4-carboxylic esters (107), $R^1 = COOR$, $R^3 = Ar$, almost quantitatively.



(107), R^1 = H, C_6H_5, CO_2R; R^3 = Alkyl, Aryl
(113), $R^1 = CO_2C_2H_5$, R^3 = OAlkyl
(114), $R^1 = SC_6H_5$, R^3 = H
(115), $R^1 = SO_2Ar$, R^3 = Aryl
(116), R^1 = H, C_6H_5; $R^3 = C{\equiv}C{-}R$ [101]
(117), $R^1 = CO_2R$, C_6H_5; $R^3 = -CH{-}CH{-}C_6H_5$ [59]
(118), R^1 =  , $R^3 = CH_3$ [28]

Metalated isocyanides (2) have so far been used for the synthesis of oxazoles with a free position 4 and their 4-alkoxycarbonyl, 5-alkyl, and 5-aryl derivatives (107)[34,100,42,43], as well as 5-arylthio- (114)[53,34] and 5-arenesulfonyloxazoles (115)[50] by the use of (21) and (23), respectively[131]. The reaction of chloroformic esters or diethyl carbonate with (16a) gives 5-alkoxyoxazole-4-carboxylic esters (113)[100].

The "decomposition" of lithiated ethyl isocyanoacetate (16a) that begins above 0 °C occurs as an ester condensation, proceeding by way of ethyl 2,4-diisocyanoacetoacetate (119)[102] and leading to the oxazole (120)[60]. Alongside this reaction there occurs an intramolecular cyclization to 5-ethoxyoxazole, a reaction that is observed to a small extent even on distillation of other α-isocyanoalkanoic esters[103].

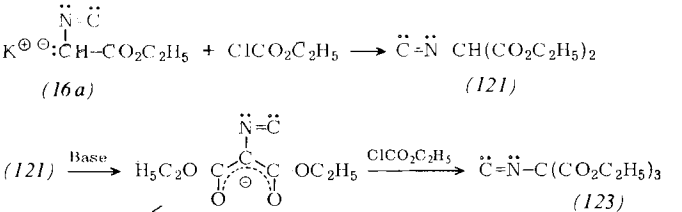


(16a) (119) (120)

Ethyl chloroformate[99] and (16a) always give rise to ethyl 5-ethoxyoxazole-4-carboxylate (113)[104]; the isocyanomalonic ester anion (122) can, however, be trapped by alkyl halides (cf. Section 6.2).

6.2. 2-Isocyanoalkanoic and 2-Isocyano-3-oxoalkanoic Esters; Synthesis of Amino Acids

The potassium salt of (122), produced *in situ* from potassium isocyanoacetate (16a) and ethyl chloroformate[99], reacts with alkyl bromides and iodides in boiling tetrahydrofuran to give the esters (124) and thus, like the alkali metal salts of *N*-formylaminomalonic esters, can be used for amino acid synthesis. Further reaction of (122) with the chloroformic ester gave triethyl isocyanomethanetricarboxylate (123)[99] (60% yield).

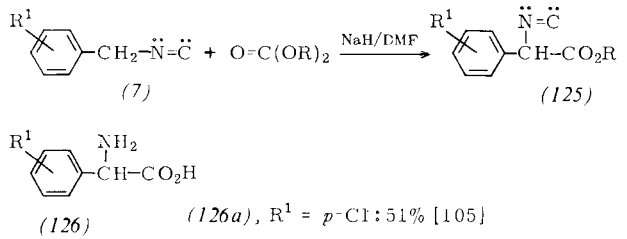


(16a) (121) (123) (122) (113) (124)

(124a), $R^2 = CH_2{-}CH{=}CH_2$: 75% [99]

Ring-substituted α-isocyanophenylacetic esters (125) have been synthesized from benzyl isocyanides (7) and dialkyl carbonate (dimethylformamide/sodium hydride, 20 °C)[22,105]

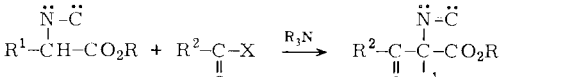
and hydrolyzed to phenylglycines *(126)* in 50—60% overall yield.



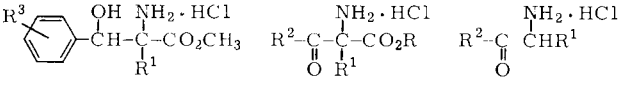
(7) *(125)*

(126) *(126a)*, R^1 = p-Cl: 51% [105]

By acylation of α-monoalkyl-substituted α-isocyanoalkanoic esters *(15)* with aroyl chlorides, *Matsumoto et al.*[42,43] prepared the 2-isocyano-3-oxoalkanoic esters *(127)*, which on hydrogenation and acid alcoholysis were converted stereoselectively into ring-substituted *erythro*-phenylserine methyl ester by hydrochloride *(128)*[88]. With methanolic hydrochloric acid the esters *(127)* give methyl 2-amino-3-oxoalkanoate hydrochlorides *(129)*, which when heated with aqueous hydrochloric acid are hydrolyzed and decarboxylated to 2-amino ketone hydrochlorides *(130)*[42,43].



(15) *(127)*

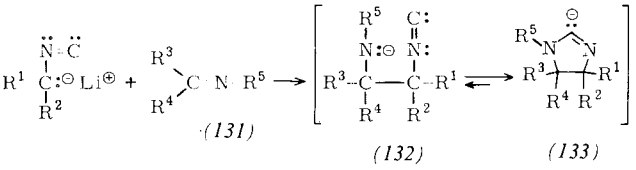


(128) *(129)* *(130)*

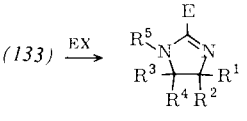
7. Reactions with Heteroanalogous Carbonyl Compounds

7.1. Reaction with Azomethines; Pyrroline Synthesis

So far as has yet been studied, only particularly nucleophilic lithioalkyl isocyanides add to azomethines *(131)*; examples are lithiomethyl *(4a)* and lithiobenzyl isocyanide *(8a)*[106]. The as yet untrapped adduct *(132)* cyclizes to the imidazolinyl anion *(133)*, which on protonation by acids affords a 2-imidazoline *(134)*; or the anion can be further substituted, in position 2, by other electrophiles such as carbonyl compounds or alkylating agents, to give compounds *(135)* or *(136)* respectively[106].



(131) *(132)* *(133)*



(134), E = H

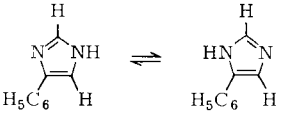
(134a), E = R^1 = R^2 = R^3 = H, R^4 = C_6H_5, R^5 =  : 77% [106]

(135), E = R^6R^7COH

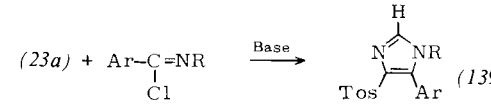
(136), E = Alkyl

7.2. Reactions with Nitriles, Imidoyl Chlorides, and Dithio Acid Esters; Synthesis of Imidazoles and Thiazoles

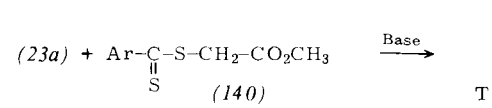
Reaction of metalated isocyanides with nitrogen or sulfur derivatives of carboxylic acids gives imidazoles and thiazoles, analogously to the formation of oxazoles (cf. Section 6.1). 4(5)-Phenylimidazole *(137)* was obtained in 40% yield from lithiomethyl isocyanide *(4a)* and benzonitrile[107]. *van Leusen et al.* synthesized 5-toluenesulfonylimidazole *(139)*[108] and 4-toluenesulfonylthiazole *(141)*[109] from toluenesulfonylmethyl isocyanide *(23a)* and, respectively, areneimidoyl chlorides *(138)* and arenecarbodithioates *(140)*.



(137)



(138) *(139a)*, Ar = C_6H_5, R =  : 80% [108]

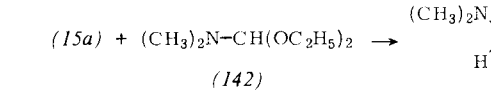


(140) *(141)*

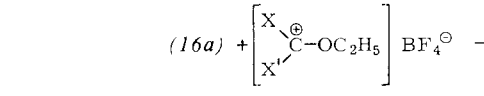
(141a), Ar = C_6H_5 : 53% [109]

7.3. Reaction with Amide Acetals; Synthesis of 3-Hetero-substituted 2-Isocyanoacrylic Esters

Ethyl isocyanoacetate *(15a)* reacts with *N,N*-dimethylformamide acetal *(142)*[110] at room temperature even without the addition of a base to yield 78% of ethyl 3-dimethylamino-2-isocyanoacrylate *(143)*[111] (presumably in the (*Z*)-configuration).

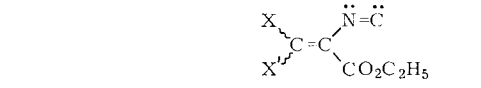


(142) *(143)*



(144a), X = X' = $N(CH_3)_2$

(144b), X = $N(CH_3)_2$, X' = OC_2H_5



(145a), X = X' = $N(CH_3)_2$; 26% [111]

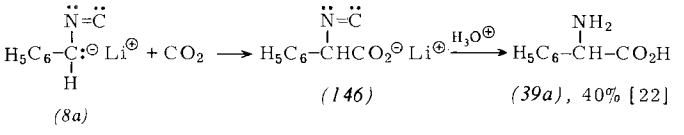
(145b), X = $N(CH_3)_2$, X' = OC_2H_5 : 14% [111]

3,3-Bishetero-substituted 2-isocyanoacrylic esters *(145a)* and *(145b)* are products of the reaction of ethyl isocyanopotassioacetate *(16a)* with the resonance-stabilized carbenium tetrafluoroborates *(144a)* and *(144b)*, respectively[111], although in poor yields.

8. Reaction with Heterocumulenes

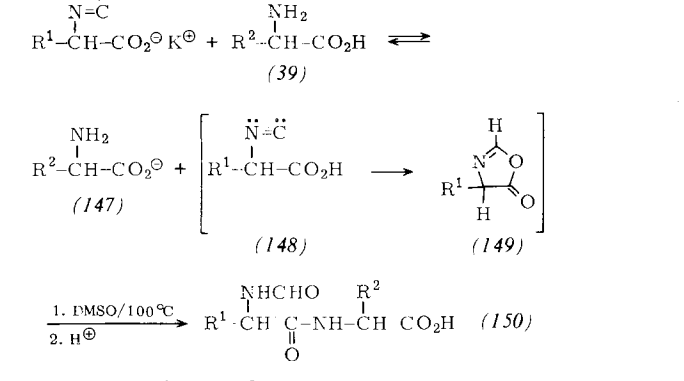
8.1. Reaction with Carbon Dioxide; α-Isocyanoalkanecarboxylates

Isocyanobenzyllithium *(8a)* gave on carboxylation[112] the isocyano carboxylate *(146)*[113, 22], which without isolation was hydrolyzed by acid to phenylglycine (yield 40%). No preparative importance attaches to this reaction, however, as alkoxycarbonylation with carbonic esters (cf. Section 6.2) is preferable for the preparation of amino acids. Salts of the type *(146)* are more simply obtained by alkaline hydrolysis of ethyl[114, 76], methyl, or trimethylsilyl esters[115] under mild conditions. Careful acidification in the absence of moisture leads to the free isocyanoalkanoic acids *(148)*, which on being warmed above 30°C pass into the 2-oxazolin-5-ones *(149)*, which are extremely sensitive to hydrolysis[114].



(8a) *(146)* *(39a)*, 40% [22]

When equimolar amounts of potassium isocyanoacetate or α-isocyanopropionate and amino acids are heated in dimethyl sulfoxide (2—5 h, 100°C), the potassium salts of *N*-formyldipeptides *(150)* are formed[114]; these can be converted into the acids by acidic ion-exchangers. The essential intermediate for this reaction is the oxazolinone *(149)*, which acylates the amino acid anion *(147)*.

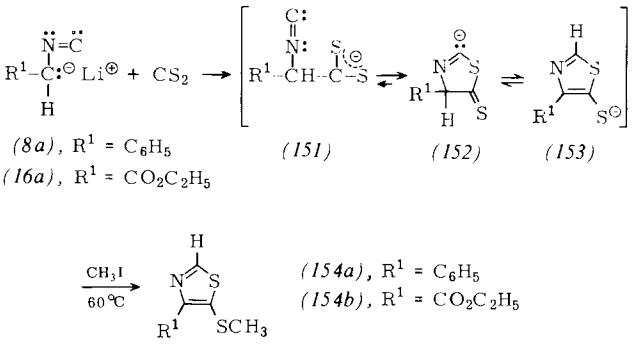


(39) *(147)* *(148)* *(149)*

(150a), R^1 = H, R^2 = $-CH_2-CH_2-S-CH_3$: 80% [114]

8.2. Reactions with Carbon Disulfide, Isocyanates, and Isothiocyanates

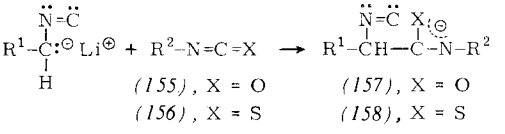
Lithiated benzyl isocyanide *(8a)* and ethyl isocyanoacetate *(16a)* add to carbon disulfide already at −60°C, giving α-isocyanoalkanedithioates *(151)*[111]. However, unlike the carboxylates of type *(146)*, these products are unstable; they cyclize and tautomerize to 5-thiazolethiolates *(153)*, which have been trapped with alkyl halides. For example, after reaction with methyl iodide, the 5-methylthiothiazoles *(154a)* and *(154b)* have been isolated, in 24 and 49% yields respectively.



(8a), R^1 = C_6H_5 *(151)* *(152)* *(153)*
(16a), R^1 = $CO_2C_2H_5$

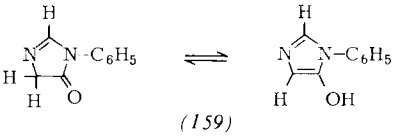
(154a), R^1 = C_6H_5
(154b), R^1 = $CO_2C_2H_5$

The interaction of lithiated isocyanides and isocyanates *(155)* or isothiocyanates *(156)* also begins with 1,2-addition to the heterocumulene system, giving rise to resonance-stabilized carboxamide *(157)* or carbothioamide anions *(158)*, respectively[111]. According to whether the free electron pair of (a)



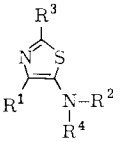
(155), X = O *(157)*, X = O
(156), X = S *(158)*, X = S

the nitrogen or (b) the oxygen or sulfur combines at the electron sextet of the isocyanide-carbon atoms, there result (a) imidazoles or (b) oxazoles or thiazoles. For example, 3-phenyl-1-imidazolin-4-one *(159)* is obtained in 30% yield from lithiomethyl isocyanide *(4a)* and phenyl isocyanate *(155)*, R^2=C_6H_5[107], whereas the corresponding adduct



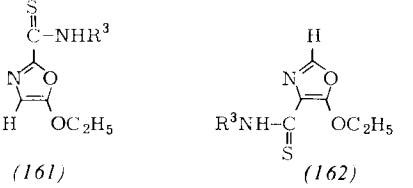
(159)

(160a), R^1 = H, R^2 = C_6H_5,
R^3 = R^4 = H : 31% [111]
(160b), R^1 = R^2 = C_6H_5,
R^3 = R^4 = H : 44% [111]
(160c), R^1 = H, R^2 = CH_3,
R^3 = R^4 = $-\overset{\overset{S}{\|}}{C}-NHCH_3$: 24% [111]
(160d), R^1 = C_6H_5, R^2 = CH_3,
R^3 = H, R^4 = $-\overset{\overset{S}{\|}}{C}-NHCH_3$: 11% [111]



(160)

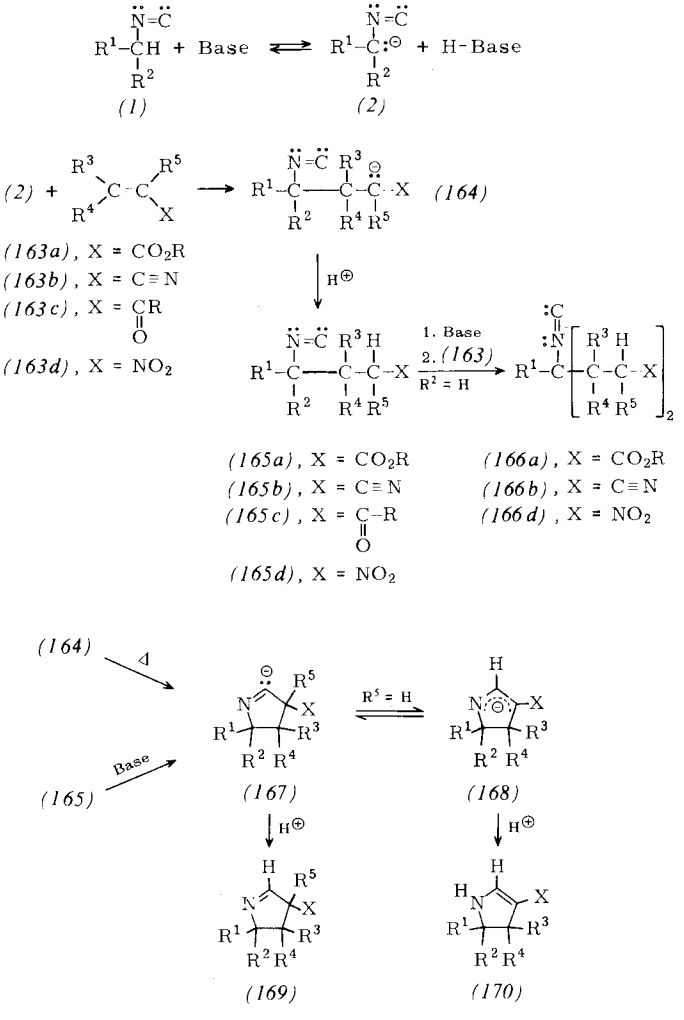
(158) from *(4a)* and phenyl isothiocyanate *(156)*, R^2=C_6H_5, cyclizes on sulfur and gives the 5-aminothiazole *(160a)*. Methyl isothiocyanate, which is more prone to addition, reacts inhomogeneously: it yields mainly more highly thiocarbamoylated thiazoles *(160c)* and *(160d)*. Surprisingly, the reaction of ethyl isocyanolithioacetate *(16a)* with isothiocyanates gives not thiazoles but oxazolethiocarbamides of structures *(161)* or *(162)*[111].



(161) *(162)*

9. Addition to Activated Olefins

In protic media, under base catalysis, isocyanides that have relatively acidic α-protons undergo Michael addition[116] to activated olefins *(163)* such as acrylic esters and nitriles *(163a)* and *(163b)*, α,β-unsaturated ketones *(163c)*, and nitroolefins *(163d)*. On protonation the adducts *(164)* give isocyanides with extended chains; when heated, the adducts cyclize to 1-pyrrolinyl anions *(167)* which, when $R^5 = H$, tautomerize to 2-pyrrolinyl anions *(168)* and thence on protonation afford 1- or 2-pyrrolines *(169)* or *(170)*.



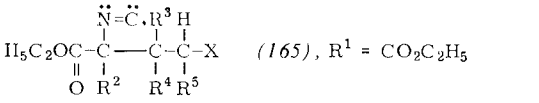
If the monoadduct *(165)* carries a hydrogen α to the isocyanide group it is able to take up a second olefin molecule to give the bisadduct *(166)*, but the resulting proportions of *(165)* to *(166)* can be controlled within only narrow limits by varying the molar ratio of the isocyanide to the olefin.

Particularly reactive Michael components, *e.g.* acrylonitrile and ethyl acrylate, favor the formation of the bisadducts; olefins that are monosubstituted in the β-position can be converted into mono- or bisadducts at will by varying the molar ratio of the reactants, α,β- and β,β-disubstituted olefins and those that are stabilized by a conjugated phenyl group react only to the monoadduct stage.

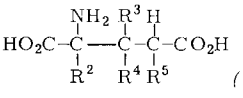
Pyrrolines *(169)* and *(170)* are obtained directly if copper(I) oxide is added as a catalyst[33], but under these conditions the direction of the reaction also can only be slightly controlled.

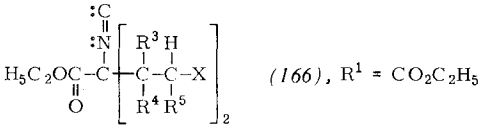
9.1. Open-chain Adducts of Types *(165)* and *(166)*; Glutamic Acid Synthesis

With α,β-unsaturated carboxylic esters *(163a)* ethyl isocyanoacetate *(15a)* or α-isocyanopropionate *(15c)* in ethanol (10—20 mol-% of sodium ethoxide) at 20—50 °C give, respectively, 30—65 % of the (chain branched) 2-isocyanoglutaric ester *(165a)*[117,118] and up to over 70 % of the bisadduct *(166a)*. Hydrolysis leads to the glutamic acid derivatives *(171)*. Analogous cyanoethylation of α,β-unsaturated nitriles *(163b)* gave products *(165b)* and *(166b)*[119,120]. Ethyl 2-isocyano-2-methyl-5-oxohexanoate is formed from *(15c)* and methyl vinyl ketone[121]. For the synthesis of 2-isocyano-4-nitroalkanoic esters *(165d)*, nitroolefins *(163d)* which polymerize rapidly in alkaline media are best brought into reaction with equimolar amounts of lithiated α-isocyanoalkanoic esters *(16)* at −78 °C[122].



$X = CO_2C_2H_5$, $R^2 = R^4 = R^5 = H$, $R^3 = CH_3$: 63% [117,118]
$X = C{\equiv}N$, $R^2 = R^5 = CH_3$, $R^3 = R^4 = H$: 86% [119,120]
$X = C(=O)-CH_3$, $R^2 = CH_3$, $R^3 = R^4 = R^5 = H$: 45% [121]
$X = NO_2$, $R^2 = R^5 = H$, $R^3 = R^4 = CH_3$: 48% [122]





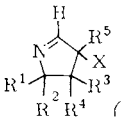
$X = CO_2C_2H_5$, $R^3 = R^4 = H$, $R^5 = CH_3$: 75% [117,118]
$X = C{\equiv}N$, $R^3 = R^4 = R^5 = H$: 55% [119,120]

9.2. Cyclization Products; Synthesis of Pyrrolines and Pyrroles

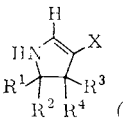
When heated with sodium ethoxide at 70—110 °C, monoadducts of type *(165)* (*in situ* or after isolation) cyclize to 1- or 2-pyrrolines *(169)* or *(170)*, respectively.

In this connection the behavior of monoadducts of types *(165a)* and *(165b)* is remarkable when there is a hydrogen atom next to the isocyanate group: their cyclization occurs by way of the ester enolate and leads to 5-alkoxyoxazoles *(172a)* and *(172b)*, respectively[118,120] (cf. Section 6.1). Nevertheless, pyrrolines result when copper(I) oxide catalysts are used[33]: *Saegusa* used benzyl isocyanide *(7a)*[33] and allyl isocyanide *(5a)*[31] as well as isocyanoalkanoic esters *(15)* to obtain pyrrolines of types *(170)*, *(173)*, and *(169)*.

If the pyrroline ring contains substituents that can be eliminated, aromatization to the pyrrole may also be achieved. Thus, *van Leusen et al.*[123] synthesized 3,4-disubstituted pyrroles *(176)* from toluenesulfonylmethyl isocyanide *(23a)* and activated olefins with sodium hydride as the base.

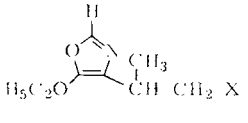


(169)

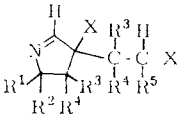


(170)

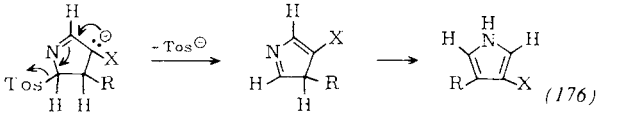
(169a), X = R^1 = $CO_2C_2H_5$, R^2 = R^5 = CH_3, R^3 = R^4 = H: 70% [118]
(169b), X = C≡N, R^1 = C_6H_5, R^2 = R^5 = CH_3, R^3 = R^4 = H: 85% [33]
(169c), X = NO_2, R^1 = $CO_2C_2H_5$, R^2 = R^3 = H, R^4 = R^5 = CH_3: 71% [122]
(170a), X = R^1 = $CO_2C_2H_5$, R^2 = CH_3, R^3 = R^4 = H: 75% [118]
(170b), X = C≡N, R^1 = $CO_2C_2H_5$, R^2 = R^3 = R^4 = H: 37% [33]



(172a), X = $CO_2C_2H_5$
(172b), X = C≡N: 50% [120]



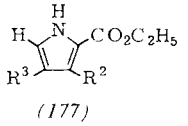
(173)



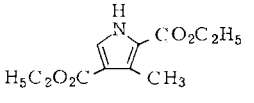
(174) (175) (176)

(176a), X = CO_2CH_3, R = H: 60% [123]
(176b), X = C≡N, R = CH_3: 50% [123]
(176c), X = C(=O)-C_6H_5, R = CH_3: 70% [123]

Formation of pyrroles with elimination of nitrite was observed on base-catalyzed cyclization of the adducts *(165d)* obtained from nitroolefins and isocyanoacetic esters; ethyl 3,4-dialkylpyrrole-2-carboxylates *(177)* were isolated[122].



(177)



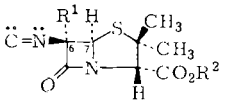
(178)

(177a), R^2 = R^3 = CH_3 71% [122]

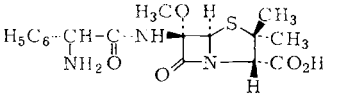
Diethyl 3-methyl-2-pyrroline-2,4-dicarboxylate was found to be a by-product in formylaminomethylenation (cf. Section 4.3.1) of acetaldehyde with ethyl isocyanolithioacetate *(16a)*[35, 36]; control experiments confirmed[62] that here ethyl 2-formylaminocrotonates of type *(71)* function as Michael components[130] for *(16a)*; the adduct cyclizes and then eliminates lithium formamide to yield *(178)*.

10. Modification of Penicillin

6- and 7-substituted penicillins and cephalosporins have aroused considerable biological interest recently[124]. *Bentley* and *Clayton*[125] started from (epimeric) 6-isocyanopenicillin benzyl ester *(179a)*, converted this *in situ* into the anion by potassium carbonate in dimethylformamide, and introduced a 6-methylthio group by means of methoxycarbonyl methyl disulfide; conversion of the sulfur group in the resulting *(179b)* into a methoxy group[126] and introduction of a D-phenylglycyl residue into the amide side chain afforded biologically active ampicillin *(180)*. The isocyanide *(179a)* reacts under the influence of bases with reactive alkyl halides (cf. Section 3.2), with acrylic esters (cf. Section 9), and with ketones (cf. Sections 4 and 5) to yield 6-alkyl-6-isocyanopenicillinic



(179a), R^1 = H (mixture of α and β), R^2 = CH_2–C_6H_5
(179b), R^1 = SCH_3
(179c), R^1 = CH_2 C_6H_5
(179d), R^1 = CH_2–CH_2–$CO_2CH_2C_6H_5$
(179e), R^1 = $C(CH_3)_2$(OH)



(180)

esters *(179c)*, *(179d)*, and *(179e)* in the α-configuration. Aqueous *p*-toluenesulfonic acid has proved valuable for converting the isocyano group into an amino group[125].

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[1] Cf. *P. Kurtz* in Houben-Weyl-Müller: Methoden der organischen Chemie. Thieme, Stuttgart 1952, 4th Edit., Vol. 8, p. 349.

[2] *U. Schöllkopf* and *F. Gerhart*, Angew. Chem. *80*, 842 (1968); Angew. Chem. internat. Edit. 7, 805 (1968).

[3] Former reviews: a) *U. Schöllkopf*, Angew. Chem. *82*, 795 (1970); Angew. Chem. internat. Edit. 9, 763 (1970); b) *U. Schöllkopf* in Houben-Weyl-Müller: Methoden der Organischen Chemie. Thieme, Stuttgart 1970, 4th Edit., Vol. 13/1, p. 234.

[4] The chemistry of isocyanides has hitherto been limited largely to α-addition of the isocyano group; review: *I. Ugi*: Isonitrile Chemistry. Academic Press, New York 1971.

[5] *P. Hoffmann, D. Marquarding, H. Kliimann,* and *I. Ugi* in *S. Patai:* The Chemistry of the Cyano Group. Interscience, New York 1970, p. 853.

[6] *I. Ugi, U. Fetzer, U. Eholzer, H. Knupfer,* and *K. Offermann,* Angew. Chem. 77, 492 (1965); Angew. Chem. internat. Edit. *4*, 472 (1965).

[7] *I. Ugi* and *R. Meyr,* Angew. Chem. *70*, 702 (1958); *I. Ugi, R. Meyr, M. Lipinski, F. Bodesheim,* and *F. Rosendahl,* Org. Synth. *41*, 13 (1961); *F. Lautenschläger* and *G. F. Wright,* Can. J. Chem. *41*, 863 (1963); *K. Pilgram* and *F. Korte,* Tetrahedron Lett. *1966*, 881.

[8] *I. Hagedorn* and *H. Tönjes,* Pharmazie *11*, 409 (1956); *12*, 567 (1957); *W. R. Hertler* and *E. J. Corey,* J. Org. Chem. *23*, 1221 (1958); *M. Lipp, F. Dallacker,* and *T. Meier zu Köcker,* Monatsh. Chem. *90*, 41 (1959); *I. Hagedorn, U. Eholzer,* and *A. Lüttringhaus,* Chem. Ber. *93*, 1584 (1960); *J. Casanova, R. E. Schuster,* and *N. D. Werner,* J. Chem. Soc. *1963*, 4280.

[9] *R. Appel, R. Kleinstück,* and *K.-D. Ziehn,* Angew. Chem. *83*, 143 (1971); Angew. Chem. internat. Edit. *10*, 132 (1971).

[10] *H. M. Walborsky* and *G. E. Niznik,* J. Org. Chem. *37*, 187 (1972); *G. E. Niznik, W. H. Morrison, III,* and *H. M. Walborsky,* Org. Synth. *51*, 31 (1971).

[11] *W. P. Weber* and *G. W. Gokel,* Tetrahedron Lett. *1972*, 1637; *W. P. Weber, G. W. Gokel,* and *I. K. Ugi,* Angew. Chem. *84*, 587 (1972); Angew. Chem. internat. Edit. *11*, 530 (1972).

[12] *A. W. Hofmann,* Ann. Chem. Pharm. *144*, 114 (1867).

[13] *F. Sachs* and *H. Loevy,* Ber. Deut. Chem. Ges. *37*, 874 (1904); *H. Gilman* and *L. C. Heckert,* Bull. Soc. Chim. Fr. [4] *43*, 224 (1928); *I. Ugi* and *U. Fetzer,* Chem. Ber. *94*, 2239 (1961).

[14] *H. M. Walborsky* and *G. E. Niznik,* J. Amer. Chem. Soc. *91*, 7778 (1969); *H. M. Walborsky, G. E. Niznik,* and *M. P. Periasamy,* Tetrahedron Lett. *1971*, 4965; *M. P. Periasamy* and *H. M. Walborsky,* J. Org. Chem. *39*, 611 (1974).

[15] *H. M. Walborsky, W. H. Morrison, III,* and *G. E. Niznik,* J. Amer. Chem. Soc. *92*, 6675 (1970); *G. E. Niznik, W. H. Morrison, III,* and *H. M. Walborsky,* J. Org. Chem. *39*, 600 (1974); *N. Hirowatari* and *H. M. Walborsky, ibid. 39*, 604 (1974); *G. E. Niznik* and *H. M. Walborsky, ibid. 39*, 608 (1974).

[16] The bonding in organolithium compounds is complicated and varies according to the alkyl group and the solvent. For simplicity the lithiated isocyanides are here represented ionically in their structural formulas; cf. *U. Schöllkopf* in [3b], p. 7; some recent papers are cited in: *W. H. Glaze,* J. Organometal. Chem. *68*, 1 (1974).

[17] *F. Gerhart* and *U. Schöllkopf,* Tetrahedron Lett. *1968*, 6231.

[18] *R. Harms,* Dissertation, Universität Göttingen, planned for 1975.

[19] Cf. *D. J. Cram:* Fundamentals of Carbanion Chemistry. Academic Press, New York 1965, p. 20.

[20] *P. Beak* and *R. Farney,* J. Amer. Chem. Soc. *95*, 4771 (1973).

[21] *R. Harms,* Diplomarbeit, Universität Göttingen 1972.

[22] *K. Matsumoto, M. Suzuki,* and *M. Miyoshi,* J. Org. Chem. *38*, 2094 (1973).

[23] *U. Schöllkopf* and *K. Hantke,* unpublished.

[24] *R. A. Olofson* and *C. M. Dougherty,* J. Amer. Chem. Soc. *95*, 582 (1973).

[25] *U. Schöllkopf* and *R. Harms,* unpublished.

[26] *W. A. Böll, F. Gerhart, A. Nürrenbach,* and *U. Schöllkopf,* Angew. Chem. *82*, 482 (1970); Angew. Chem. internat. Edit. *9*, 458 (1970).

[27] *F. Gerhart,* unpublished.

[28] *F. Kienzle,* Helv. Chim. Acta *56*, 1671 (1973).

[29] *R. Thoms,* Dissertation, Universität Göttingen 1974.

[30] *U. Schöllkopf* and *R. Jentsch,* Angew. Chem. *85*, 355 (1973); Angew. Chem. internat. Edit. *12*, 323 (1973).

[31] *T. Saegusa, I. Murase,* and *Y. Ito,* Bull. Soc. Chem. Jap. *45*, 830 (1972).

[32] *U. Schöllkopf* and *I. Hoppe,* unpublished.

[33] *T. Saegusa, Y. Ito, H. Kinoshita,* and *S. Tomita,* J. Org. Chem. *36*, 3316 (1971).

[34] *U. Schöllkopf, R. Schröder, E. Blume,* and *I. Hoppe,* Liebigs Ann. Chem. *1974*, in press.

[35] *U. Schöllkopf, F. Gerhart,* and *R. Schröder,* Angew. Chem. *81*, 701 (1969); Angew. Chem. internat. Edit. *8*, 672 (1969).

[36] *U. Schöllkopf, F. Gerhart, R. Schröder,* and *D. Hoppe,* Liebigs Ann. Chem. *766*, 116 (1972).

[37] *U. Schöllkopf* and *D. Hoppe,* Angew. Chem. *82*, 253 (1970); Angew. Chem. internat. Edit. *9*, 236 (1970).

[38] *U. Schöllkopf* and *D. Hoppe,* Liebigs Ann. Chem. *1973*, 799.

[39] *U. Schöllkopf, D. Hoppe,* and *R. Jentsch,* Angew. Chem. *83*, 357 (1971); Angew. Chem. internat. Edit. *10*, 331 (1971).

[40] *D. Hoppe* and *U. Schöllkopf,* Angew. Chem. *82*, 290 (1970); Angew. Chem. internat. Edit. *9*, 300 (1970); *U. Schöllkopf, D. Hoppe,* and *R. Jentsch,* Chem. Ber., in press.

[41] *D. Hoppe* and *U. Schöllkopf,* Liebigs Ann. Chem. *763*, 1 (1972).

[42] *M. Suzuki, T. Iwasaki, K. Matsumoto,* and *K. Okumura,* Synth. Commun. *2*, 237 (1972).

[43] *M. Suzuki, T. Iwasaki, M. Miyoshi, K. Okumura,* and *K. Matsumoto,* J. Org. Chem. *38*, 3571 (1973).

[44] *K. Hantke,* Dissertation, Universität Göttingen 1973; *K. Hantke, U. Schöllkopf,* and *H.-H. Hausberg,* Liebigs Ann. Chem., in press.

[45] *R. West* and *G. A. Gornowicz,* J. Organometal. Chem. *25*, 385 (1970).

[46] *U. Schöllkopf* and *E. Blume,* Tetrahedron Lett. *1973*, 629.

[47] *U. Schöllkopf* and *R. Schröder,* Angew. Chem. *84*, 289 (1972); Angew. Chem. internat. Edit. *11*, 311 (1972).

[48] *U. Schöllkopf, R. Schröder,* and *E. Blume,* Liebigs Ann. Chem. *766*, 130 (1972).

[49] *A. M. van Leusen, G. J. M. Boerma, R. B. Helmholdt, H. Siderius,* and *J. Strating,* Tetrahedron Lett. *1972*, 2367.

[50] *A. M. van Leusen, B. E. Hoogenboom,* and *H. Siderius,* Tetrahedron Lett. *1972*, 2369.

[51] *O. H. Oldenziel* and *A. M. van Leusen,* Tetrahedron Lett. *1972*, 2777.

[52] *U. Schöllkopf* and *R. Schröder,* Tetrahedron Lett. *1973*, 633.

[53] *U. Schöllkopf, R. Schröder,* and *D. Stafforst,* Liebigs Ann. Chem. *1974*, in press.

[54] *H. Hennecke,* Diplomarbeit, Universität Göttingen 1973.

[55] For conversion of isocyanides into formamides and for deformylation see [39] and literature cited therein.

[56] For monoalkylation of carbanions see: *H. O. House:* Modern Synthetic Reactions. Benjamin, Menlo Park, Calif. 1972, 2nd Edit., p. 510, and literature cited therein.

[57] *M. Suzuki, K. Matsumoto, T. Iwasaki,* and *K. Okumura,* Chem. Ind. (London) *1972*, 687.

[58] For copper-catalyzed α-addition of isocyanides see: *T. Saegusa, Y. Ito, S. Kobayashi,* and *K. Hirota,* J. Amer. Chem. Soc. *89*, 2240 (1967); *T. Saegusa, Y. Ito,* and *S. Kobayashi,* Tetrahedron Lett. *1968*, 935; and ref. [4], p. 67.

[59] *K. Madawinata,* Diplomarbeit, Universität Göttingen 1974.

[60] *R. Jentsch,* Dissertation, Universität Göttingen 1973.

[61] *F. G. Bordwell, H. M. Andersen,* and *B. M. Pitt,* J. Amer. Chem. Soc. *76*, 1082 (1954); *R. D. Schuetz* and *R. L. Jakobs,* J. Org. Chem. *26*, 3467 (1961).

[62] For a similar equilibrium between the cyclic and the open-chain anion of 2-lithiated 5,6-dihydro-4*H*-1,3-oxazines see: *A. I. Meyers* and *H. W. Adickes,* Tetrahedron Lett. *1969*, 5151.

[63] The original isomers ratio can be shifted to *ca.* 3:1 in favor of *cis-(59a)* by double lithiation and protonation: *K.-H. Scheunemann,* Diplomarbeit, Universität Göttingen 1974.

[64] *I. Hagedorn, U. Eholzer,* and *A. Lüttringhaus,* Chem. Ber. *93*, 1584 (1960); *I. Hagedorn* and *E. Etling,* Angew. Chem. *73*, 26 (1961).

[65] *D. S. Matteson* and *I. Bailey,* J. Amer. Chem. Soc. *90*, 3761 (1968).

[66] *U. Schöllkopf* and *P. Böhme,* Angew. Chem. *83*, 490 (1971); Angew. Chem. internat. Edit. *10*, 491 (1971).

[67] *R. B. Woodward* and *R. Hoffmann,* Angew. Chem. *81*, 777 (1969); Angew. Chem. internat. Edit. *8*, 781 (1969).

[68] *M. J. S. Dewar,* Angew. Chem. *83*, 859 (1971); Angew. Chem. internat. Edit. *10*, 761 (1971).

[69] *U. Schöllkopf, I. Hoppe,* and *K.-H. Scheunemann,* unpublished.

[70] Reviews: *J. Boutagy* and *R. Thomas,* Chem. Rev. *74*, 87 (1974); *U. Schöllkopf,* Angew. Chem. *71*, 260 (1959); also [3b] and previous reviews cited therein.

[71] For analogous ring openings see [36]; also *D. Hoppe,* Angew. Chem. *85*, 660 (1973); Angew. Chem. internat. Edit. *12*, 658 (1973).

[72] *P. Markusch,* Dissertation, Universität Göttingen 1969.

[73] *U. Schöllkopf* and *K. Hantke,* unpublished; *(71c)* was obtained only in the indicated configuration; *G. Haffer,* Berlin, personal communication.

[74] Review: *H. E. Carter,* Org. React. *3*, 198 (1946).

[75] *T.-P. Dang* and *H. B. Kagan,* Chem. Commun. *1971*, 481; *H. P. Kagan* and *T.-P. Dang,* J. Amer. Chem. Soc. *94*, 6429 (1972); *W. S. Knowles, M. J. Sabacky,* and *B. D. Vineyard, ibid. 94*, 10 (1972).

[76] *U. Schöllkopf, R. Harms,* and *D. Hoppe,* Liebigs Ann. Chem. *1973*, 611.

[77] *U. Schöllkopf* and *R. Meyer,* Angew. Chem., in press.

[78] *U. Schöllkopf* and *D. Hoppe,* Angew. Chem. *85*, 1102 (1973); Angew. Chem. internat. Edit. *12*, 1006 (1973).

[79] *A. K. Bose, G. Spiegelman,* and *M. S. Manhas,* J. Amer. Chem. Soc. *90*, 4506 (1968).

[80] *A. J. Brink, J. Coetzer, A. Jordaan,* and *G. J. Lourens,* Tetrahedron Lett. *1972*, 5353; *A. J. Brink* and *A. Jordan,* Carbohyd. Res. *34*, 1 (1974).

[81] *H. Böhme* and *G. Fuchs,* Chem. Ber. *103*, 2775 (1970).

[82] *T. Olijnsma, J. B. F. N. Engberts*, and *J. Strating*, Rec. Trav. Chim. Pays-Bas *91*, 209 (1972).

[83] *U. Schöllkopf* and *R. Schröder*, Angew. Chem. *85*, 402 (1973); Angew. Chem. internat. Edit. *12*, 407 (1973).

[84] *O. H. Oldenziel* and *A. M. van Leusen*, Synth. Commun. *2*, 281 (1972).

[85] For recognition of the relative configuration only one enantiomer is shown.

[86] Review: *J. A. Frump*, Chem. Rev. *71*, 483 (1971).

[87] *D. Hoppe* and *U. Schöllkopf*, Angew. Chem. *84*, 435 (1972); Angew. Chem. internat. Edit. *11*, 432 (1972).

[88] *M. Suzuki, T. Iwasaki, K. Matsumoto*, and *K. Okumura*, Chem. Ind. (London) *1973*, 228.

[89] *Y. Hartleben*, Gronau, personal communication.

[90] *R. Damico* and *J. M. Nicholson*, J. Org. Chem. *38*, 3057 (1973).

[91] *U. Schöllkopf* and *D. Hoppe*, Angew. Chem. *82*, 483 (1970); Angew. Chem. internat. Edit. *9*, 459 (1970).

[92] *A. I. Meyers* and *E. W. Collington*, J. Amer. Chem. Soc. *92*, 6676 (1970).

[93] *H.-H. Hausberg*, Diplomarbeit, Universität Göttingen 1973.

[94] *F. Becke* and *P. Pässler*, Liebigs Ann. Chem. *735*, 27 (1970).

[95] *W. Jung*, Diplomarbeit, Universität Göttingen 1974.

[96] *O. H. Oldenziel* and *A. M. van Leusen*, Tetrahedron Lett. *1974*, 163.

[97] *O. H. Oldenziel* and *A. M. van Leusen*, Tetrahedron Lett. *1974*, 167.

[98] *I. Hagedorn* and *E. Etling*, Angew. Chem. *73*, 26 (1961).

[99] *R. Schröder*, Dissertation, Universität Göttingen 1972.

[100] *U. Schöllkopf* and *R. Schröder*, Angew. Chem. *83*, 358 (1971); Angew. Chem. internat. Edit. *10*, 333 (1971).

[101] *E. Eilers*, Dissertation, Universität Göttingen 1974.

[102] *D. Marquarding* and *I. Ugi*, unpublished work, cited in ref. [4], p. 237.

[103] *U. Schöllkopf, R. Schröder, D. Hoppe*, and *R. Jentsch*, unpublished.

[104] Dehydration of diethyl formylaminomalonate also affords the 5-alkoxyoxazole; *F. Gerhart*, unpublished work.

[105] It is surprising that the esters *(125)* do not at least partially cyclize under the alkaline reaction conditions since ethyl α-isocyanophenylacetate gives mainly 5-ethoxy-4-phenyloxazole on distillation: *D. Hoppe*, unpublished work.

[106] *P. Böhme*, Dissertation, Universität Göttingen 1974.

[107] *E. Eilers*, Diplomarbeit, Universität Göttingen 1970.

[108] *A. M. van Leusen* and *O. H. Oldenziel*, Tetrahedron Lett. *1972*, 2373.

[109] *O. H. Oldenziel* and *A. M. van Leusen*, Tetrahedron Lett. *1972*, 2777.

[110] *H. Meerwein, W. Florian, N. Schön*, and *G. Stopp*, Liebigs Ann. Chem. *641*, 1 (1961).

[111] *P.-H. Porsch*, Dissertation, Universität Göttingen 1973.

[112] Reviews: *G. Gilman* and *J. W. Morton*, Org. React. *8*, 290 (1954); *R. G. Jones* and *H. Gilman*, *ibid. 6*, 358 (1951).

[113] *W. Vaalburg, J. Strating, M. G. Woldring*, and *H. Wynberg*, Synth. Commun. *2*, 423 (1972).

[114] *D. Hoppe*, unpublished.

[115] *G. Gokel, P. Hoffmann, H. Kleimann, H. Klusacek, G. Lüdke, D. Marquarding*, and *I. Ugi* in ref. [4], p. 205.

[116] Review: *H. O. House*, [56], p. 595.

[117] *U. Schöllkopf* and *K. Hantke*, Angew. Chem. *82*, 932 (1970); Angew. Chem. internat. Edit. *9*, 896 (1970).

[118] *U. Schöllkopf* and *K. Hantke*, Liebigs Ann. Chem. *1973*, 1571.

[119] *U. Schöllkopf* and *P.-H. Porsch*, Angew. Chem. *84*, 478 (1972); Angew. Chem. internat. Edit. *11*, 429 (1972).

[120] *U. Schöllkopf* and *P.-H. Porsch*, Chem. Ber. *106*, 3382 (1973).

[121] *K. Hantke*, Diplomarbeit, Universität Göttingen 1971.

[122] *D. Stafforst*, Diplomarbeit, Universität Göttingen 1971.

[123] *A. M. van Leusen, H. Siderius, B. E. Hoogenboom*, and *D. van Leusen*, Tetrahedron Lett. *1972*, 5337.

[124] *J. E. Baldwin, F. J. Urban, R. D. G. Cooper*, and *F. L. Jose*, J. Amer. Chem. Soc. *95*, 2401 (1973); *G. A. Koppel* and *R. E. Koehler*, *ibid. 95*, 2403 (1973); *R. A. Firestone* and *B. G. Christensen*, J. Org. Chem. *38*, 1436 (1973); *W. A. Slusarchyk, H. E. Applegate, P. Funke, W. Koster, M. S. Puar, M. Young*, and *J. E. Dolfini*, *ibid. 38*, 943 (1973).

[125] *P. H. Bentley* and *J. P. Clayton*, J. C. S. Chem. Comm. *1974*, 278.

[126] *W. A. Spitzner* and *T. Goodson*, Tetrahedron Lett. *1973*, 273.

[127] As recently reported, (+)-(*S*)-1-isocyano-2,2-diphenylcyclopropyllithium is configurationally stable below −50°C. It follows that mesomeric stabilization by the isocyano group plays no part; see: *H. M. Walborsky* and *M. P. Periasamy*, J. Amer. Chem. Soc. *96*, 3711 (1974).

Notes added in proof (November 21, 1974):

[128] Very recently the first vinyl isocyanide *(63)* has been metalated: *E*/*Z*-β-styryl isocyanide *(63a)* was lithiated with *n*-butyllithium in tetrahydrofuran/*n*-pentane/diethyl ether (4:1:1) at −110°C (trapped by methyl iodide, trimethylchlorosilane, carbonyl compounds, and carbon dioxide); *U. Schöllkopf* and *D. Stafforst*, unpublished.

[129] 3- and 4-pyridylmethyl isocyanide were metalated with potassium *tert*-butoxide at −70°C and converted by carbonyl compounds into oxazolines of type *(59)*, which underwent ring opening to *N*-(1-pyridyl-1-alkenyl)-formamides (3- or 4-pyridyl instead of CO_2R in *(71)*) on warming to 0°C in the presence of excess base. The reaction sequence with subsequent acid hydrolysis affords an "*Eintopf*" synthesis of 3- or 4-pyridylalkyl (or aryl)ketones of type *(76)* in yields of 60 to 80%; *U. Schöllkopf, E. Eilers*, and *K. Hantke*, unpublished.

[130] See also *M. Suzuki, M. Miyoshi*, and *K. Matsumoto*, J. Org. Chem. *39*, 1980 (1974).

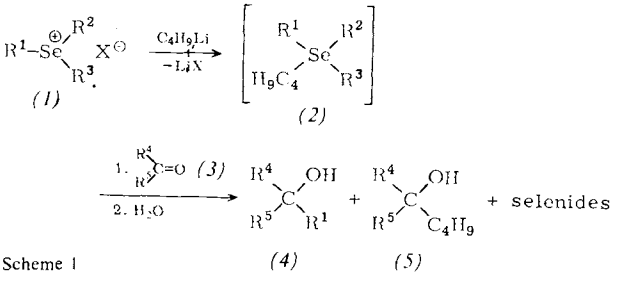
[131] A synthesis of 3-amino-4-hydroxycumarins from *(15)* *via* oxazoles is reported by: *K. Matsumoto, M. Suzuki, M. Miyoshi*, and *K. Okumura*, Synthesis *1974*, 500.

COMMUNICATIONS

Cleavage of Selenium Compounds by Butyllithium. A New, Regiospecific, Allyl Alcohol Synthon

By *Willy Dumont, Pierre Bayet*, and *A. Krief*[*]

In this paper, we describe the ready cleavage of selenonium salts *(1)*[1] and selenides *(6)*[2] by *n*-butyllithium; subsequent addition of a carbonyl compound to the reaction mixture affords alcohols resulting mainly from the migration of one of the substituents originally attached to the selenium.



Scheme 1

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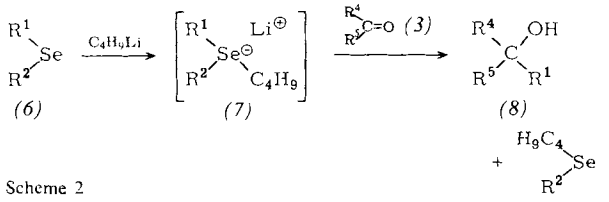
[**] On leave from CNRS (France).

Table 1. Alcohols *(4)* and *(5)* prepared according to Scheme 1 [3a]. *(1a)*, $R^1=R^2=R^3=CH_3$, X = I; *(1b)*, $R^1=R^2=C_6H_5$, $R^3=CH_3$, $X=BF_4$; *(1c)*, $R^1=C_6H_5$, $R^2=R^3=CH_3$, $X=CH_3SO_4$.

(1)	R^1	R^4	R^5	*(4)* Yield [%]	*(5)* Yield [%]
(1a)	CH_3	C_6H_5	H	54	16
(1a)	CH_3	C_6H_5	CH_3	75	—
(1a)	CH_3	n-C_6H_{13}	H	45	28
(1a)	CH_3	C_6H_5	C_6H_5	54	12
(1a)	CH_3	$-(CH_2)_2CH(t\text{-}C_4H_9)(CH_2)_2-$		40	25
(1b)	C_6H_5	C_6H_5	H	40	—
				32 [a]	
(1b)	C_6H_5	C_6H_5	CH_3	70	—
(1b)	C_6H_5	n-C_6H_{13}	H	49	
				7 [a]	—
(1c)	C_6H_5 [b]	C_6H_5	H	56	—

[a] Isolated as methyl ether.
[b] 1-Phenylethanol was also isolated in 24% yield.

In some cases, butylated alcohols were also observed, especially when trimethylselenonium iodide *(1a)* or dimethyl selenide *(6a)* were used (Tables 1 and 2).



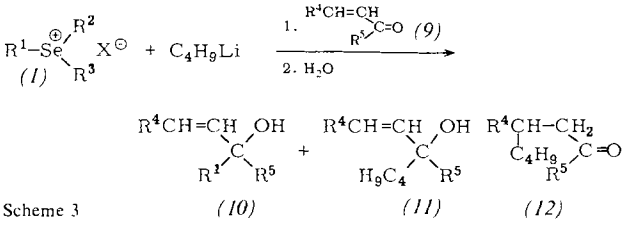
Scheme 2

Table 2. Alcohols *(8)* prepared according to Scheme 2 [3b].

(6)	R^1	R^2	R^4	R^5	*(8)*, Yield [%]
(6a)	CH_3	CH_3	C_6H_5	H	32 [a]
(6b)	C_6H_5	CH_3	C_6H_5	H	93
(6b)	C_6H_5	CH_3	n-C_6H_{13}	H	68
(6b)	C_6H_5	CH_3	C_6H_5	CH_3	27
(6c)	C_6H_5	C_6H_5	n-C_6H_{13}	H	85
(6c)	C_6H_5	C_6H_5	C_6H_5	CH_3	74
(6c)	C_6H_5	C_6H_5	C_6H_5	H	72
(6d)	C_6H_5	$C_6H_5CH_2$	C_6H_5	H	75
(6e)	$C_6H_5CH_2$	CH_3	n-C_6H_{13}	H	30 [b]
(6f)	C_6H_5	CH_2=CH−CH_2	C_6H_5	H	60

[a] 1-Phenyl-1-pentanol was also isolated in 44% yield.
[b] 2-Octanol was also detected (1–2%).

Surprisingly, the use of α,β-unsaturated carbonyl compounds *(9)* increased the proportion of butylation products (Table 3).



Scheme 3

Table 3. Allyl alcohols *(10)* and *(11)* and ketones *(12)* prepared according to Scheme 3 [3a]. *(1a)*, $R^1=R^2=R^3=CH_3$, X = I; *(1b)*, $R^1=R^2=C_6H_5$, $R^3=CH_3$, $X=BF_4$.

(1)	R^1	R^4	R^5	*(10)*	*(11)*	*(12)* Yield [%]
(1a)	CH_3	C_6H_5	C_6H_5	26.5	31.5	40.5
(1a)	CH_3	C_6H_5	H	20	42	–
(1b)	C_6H_5	C_6H_5	C_6H_5	47.5	17	–
				7 [a]		

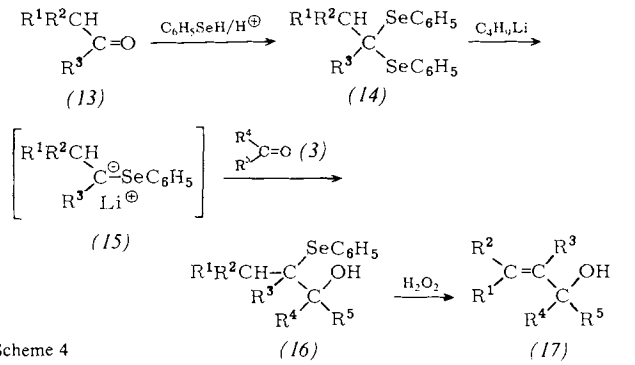
[a] Isolated as methyl ether.

Typically in *(1b)*, *(1c)* and *(6b)*, the phenyl group is transferred preferentially to the methyl group.

To account for our results, we assume that addition of butyllithium to the selenium compound *(1)* or *(6)* leads to a tetra- *(2)* or tri-substituted intermediate *(7)*[4]; subsequent migration of one of the substituents to the carbonyl compound gives rise to the alcohol.

As a synthetic application of this Se—C cleavage, we describe a new regiospecific synthesis of allyl alcohols *(17)* starting formally from two carbonyl compounds [*(13)* and *(3)*]. The key step of this synthesis is the facile cleavage of selenoacetals *(14)*[5] by *n*-butyllithium in THF (−78 °C) to give carbanions *(15)* which add a variety of aldehydes and ketones *(3)* to form β-hydroxyselenides *(16)* in good yields (Table 4).

While β-hydroxyselenides have already been obtained by the ring opening of epoxides with selenophenolate[6], cleavage of unsymmetrically substituted epoxides can furnish two different β-hydroxyselenides. Such ambiguity is avoided by our method. The exact position and nature of all of the substituents (R^1—R^5) are strictly dependent on the choice of the two carbonyl compounds.



Scheme 4

Table 4. β-Hydroxyselenides *(16)* und allyl alcohols *(17)* prepared according to Scheme 4. Yields refer to purified products [7].

	R^1	R^2	R^3	R^4	R^5	*(16)* Yield [%]	*(17)* Yield [%]
a	H	H	CH_3	C_6H_5	CH_3	67	80
b	H	H	CH_3	H	n-C_6H_{13}	70	80
c	H	H	CH_3	−$(CH_2)_5$−		78	93
d	H	H	H	H	n-C_6H_{13}	49	78
e	H	CH_3	H	H	n-C_6H_{13}	60	74 [a]

[a] We presume that the stereochemistry of the carbon-carbon double bond is mainly *trans* ($J_{H-H}=15$ Hz).

Finally, using *Sharpless*' procedure[6] the hydroxyselenides *(16a)*—*(16e)* are readily oxidized with hydrogen peroxide (THF, 1h, 25 °C) to give allyl alcohols *(17)* in high yield (Table 4). We are currently investigating the scope and stereochemistry of these reactions, as well as the use of Se—C cleavage to generate carbanions which are difficult to obtain by usual methods.

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CAS Registry numbers: *(1a)*, 7362-34-7; *(1b)*, 52724-83-1; *(1c)*, 13118-29-1; *(3)*, $R^4=C_6H_5$, $R^5=H$, 100-52-7; *(3)*, $R^4=C_6H_5$, $R^5=CH_3$, 98-86-2; *(3)*, $R^4=n$-C_6H_{13}, $R^5=H$, 111-71-7; *(3)*, $R^4=R^5=C_6H_5$, 119-61-9; *(3)*, $R^4,R^5=(CH_2)_2CH(t$-$C_4H_9)(CH_2)_2$, 98-53-3; *(3)*, $R^4,R^5=(CH_2)_5$, 108-94-1; *(6a)*, 593-79-3; *(6b)*, 4346-64-9; *(6c)*, 1132-39-4; *(6d)*, 18255-05-5; *(6e)*, 5925-78-0; *(6f)*, 14370-82-2; *(8)*, $R^1=C_6H_5CH_2$, $R^4=n$-C_6H_{13}, $R^5=H$, 19396-72-6; *(9)*, $R^4=R^5=C_6H_5$, 94-41-7; *(9)*, $R^4=C_6H_5$, $R^5=H$, 104-55-2; *(13)*, $R^1=R^2=H$, $R^3=CH_3$, 67-64-1; *(13)*, $R^1=R^2=R^3=H$, 75-07-0; *(13)*, $R^1=R^3=H$, $R^2=CH_3$, 123-38-6; *(16a)*, 53188-71-9; *(16b)*, 53188-72-0; *(16c)*, 53188-73-1; *(16d)*, 53188-74-2; *(16e)*, 53188-75-3; *(17a)*, 29290-99-1; *(17b)*, 52500-37-5; *(17c)*, 3908-31-4; *(17d)*, 21964-44-3; *(17e)*, 53188-77-5; Butyllithium, 109-72-8; Bis(phenylseleno)methane, 20343-90-2; *(4)*, $R^1=CH_3$, $R^4=C_6H_5$, $R^5=H$, 98-85-1; *(4)*, $R^1=R^5=CH_3$, $R^4=C_6H_5$, 617-94-7; *(4)*, $R^1=CH_3$, $R^4=n$-C_6H_{13}, $R^5=H$, 123-96-6; *(4)*, $R^1=CH_3$, $R^4=R^5=C_6H_5$, 599-67-7; *(4)*, $R^1=CH_3$, $R^4,R^5=(CH_2)_2CH(t$-$C_4H_9)(CH_2)_2$, 6353-54-4; *(4)*, $R^1=R^4=C_6H_5$, $R^5=H$, 91-01-0; *(4)*, $R^1=C_6H_5$, $R^4=n$-C_6H_{13}, $R^5=H$, 614-54-0; *(5)*, $R^4=C_6H_5$, $R^5=H$, 583-03-9; *(5)*, $R^4=n$-C_6H_{13}, $R^5=H$, 37493-70-2; *(5)*, $R^4=R^5=C_6H_5$, 5384-63-4; *(5)*, $R^4,R^5=(CH_2)_2CH(t$-$C_4H_9)(CH_2)_2$, 53188-79-7; *(10)*, $R^1=CH_3$, $R^4=R^5=C_6H_5$, 41231-78-1; *(10)*, $R^1=CH_3$, $R^4=C_6H_5$, $R^5=H$, 17488-65-2; *(10)*, $R^1=R^4=R^5=C_6H_5$, 4663-36-9; *(11)*, $R^4=R^5=C_6H_5$,

53188-81-1; *(11)*, $R^4=C_6H_5$, $R^5=H$, 20157-19-1; *(12)*, $R^4=R^5=C_6H_5$, 1454-57-5

[1] Unstabilized selenonium ylides can be generated by reaction of suitable bases with selenonium salts: *W. Dumont, P. Bayet,* and *A. Krief,* Angew. Chem. *86*, 308 (1974); Angew. Chem. internat. Edit. *13*, 274 (1974).

[2] Similar cleavage of some selenides has been described: a) *H. Gilman* and *R. L. Bebb,* J. Amer. Chem. Soc. *61*, 1110 (1939); b) *H. Gilman* and *F. J. Webb,* J. Amer. Chem. Soc. *71*, 4064 (1949); c) *D. Seebach* and *N. Peleties,* Angew. Chem. *81*, 465 (1969); Angew. Chem. internat. Edit. *8*, 450 (1969); d) *D. Seebach* and *N. Peleties,* Chem. Ber. *105*, 511 (1972). However, no systematic study was performed.

[3] Reaction conditions: a) To a suspension of 6 mmol of *(1)* in THF (10 ml) was added (at −78 °C, under N_2) 5.5 mmol of *n*-butyllithium in hexane (2.75 ml). After 10 min, the carbonyl compound (5 mmol in 5 ml THF) was introduced and the mixture was allowed to react for 2 h at −78 °C and 1 h at 20 °C. b) To a solution of 6 mmol of *(6)* in THF (10 ml) was added (at 0 °C, under N_2) 5.5 mmol of *n*-butyllithium in hexane (2.75 ml). After 15 min at 0 °C and 30 min at 20 °C, the carbonyl compound (5 mmol in 5 ml THF) was introduced and the mixture was allowed to react for 2 h at 20 °C.

[4] See a) *G. Wittig* and *H. Fritz,* Liebigs Ann. Chem. *577*, 41 (1962); b) *D. Hellwinkel* and *G. Farbach, ibid. 715*, 68 (1968).

[5] *D. Seebach* [2c, 2d] reported one example of this type: cleavage of bis(phenylseleno)methane with *n*-butyllithium to give phenylselenomethyllithium which was trapped by reaction with benzophenone.

[6] *K. B. Sharpless* and *R. F. Lauer,* J. Amer. Chem. Soc. *95*, 2697 (1973).

[7] Reaction conditions: To a solution of selenoketal *(14)* (5.2 mmol) in THF (10 ml) was added a solution of *n*-butyllithium (5.2 mmol) at −78 °C under N_2. After stirring for a further 1.5 h (not optimized), *(3)* (5 mmol) in THF (5 ml) was slowly introduced. The mixture was allowed to react for 2 h at −78 °C and 2 h (15 h with acetophenone) at 25 °C, hydrolyzed and worked up in the usual manner.

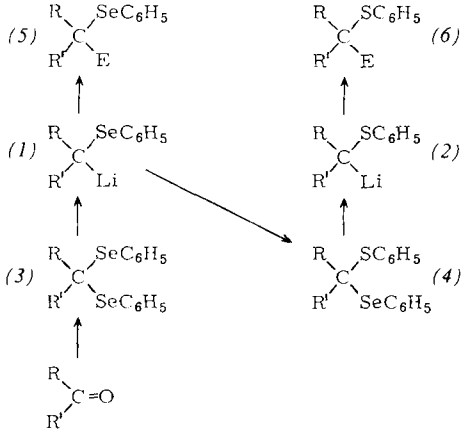
Secondary and Tertiary Phenylthio- and Phenylseleno-alkyllithium Compounds as Novel Reagents for the Formation of C—C Bonds[***]

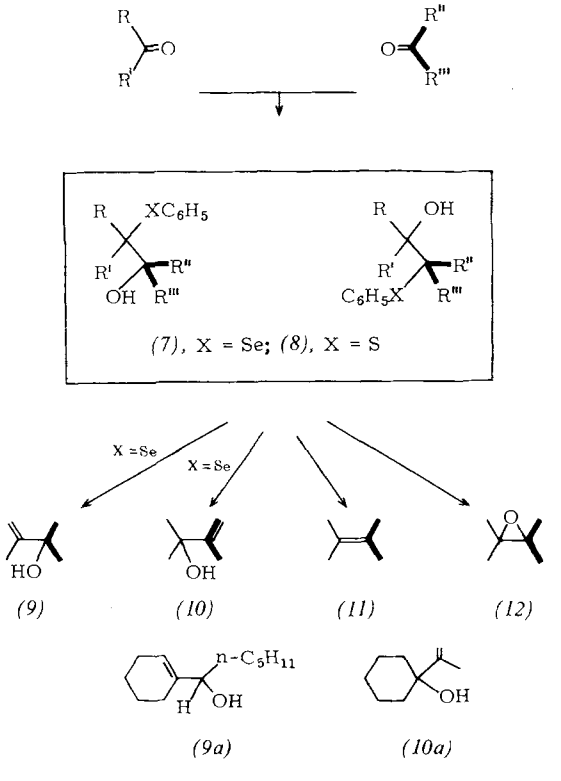
By *Dieter Seebach* and *Albert K. Beck*[*]

Because of its pronounced nucleophilic character, phenylthiomethyllithium *(2)*, R = R′ = H, which is readily accessible by metalation of thioanisol[1], has acquired considerable preparative significance as a CH_2 synthon in methylenations of carbonyl compounds to give olefins[2a] and epoxides[2b] and for the homologization of primary halides[2c]. However, a wide range of variation of the transfer group seemed to be precluded[2b] by the tendency of alkyl aryl sulfides containing higher alkyl groups to undergo *o*-metalation on reaction with *n*-butyllithium. (Ring metalation is favored thermodynamically by a factor of at least 50[3].)

We have now found C_6H_5Se/Li exchange[4], which is comparable with Br/Li exchange, to offer a kinetically controlled method for the preparation of secondary and tertiary phenylseleno- *(1)* and phenylthio-alkyllithium compounds *(2)*. The selenoacetals *(3)* obtained from aldehydes or ketones or by alkylation of *(1)*, $R=SeC_6H_5$, $R'=H$[4b] are converted into the selenium-substituted derivatives *(1)* within 15 min on treatment with *n*- or *tert*-butyllithium in THF at −80 °C. The products can be transformed by thiolation into the S, Se acetals *(4)* which yield the sulfur-substituted derivatives *(2)* on renewed transmetalation. Reaction of the organolithium compounds *(1)* or *(2)* with electrophiles furnishes the products *(5)* and *(6)* respectively (Table 1).

As can be seen from Scheme 1, the phenylseleno- *(7)* and phenylthio-alkyl alcohols *(8)* prepared with aldehydes and ketones as electrophiles are actually formed by coupling of the carbonyl C atoms of *two* aldehydes or ketones. The selenium derivatives *(7)* can be oxidized[5] to yield allyl alcohols *(9)* or *(10)*, *e.g. (9a)* from cyclohexanone and hexanal (overall yield 50%) or *(10a)* from cyclohexanone and acetone (overall yield 65%). Hence compounds of type *(1)* can be regarded as masked *vinyllithium compounds.*





Scheme 1. Transformations possible with the organolithium compounds *(1)* and *(2)* and ketones and aldehydes as electrophiles.

The olefins *(11)* and epoxides *(12)* should likewise be accessible from the selenium- *(7)*[6] or sulfur-containing alcohols *(8)*[2a, 2b] by known methods.

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[***] This work was supported by the Deutsche Forschungsgemeinschaft.

Table 1. Starting materials, yields, and physical data of compounds of types *(3)*–*(8)*, *(9a)*, and *(10a)*.

Cpd.	Prepared from	Yield [%]	NMR characterization (δ [ppm] in CCl_4, *J* [Hz])
(3), R = CH_3, R′ = H	*(1)*, R = SeC_6H_5, R′ = H, + CH_3I	95 [a]	see [4b]
(3), R = *n*-$C_{10}H_{21}$, R′ = H	*(1)*, R = SeC_6H_5, R′ = H, + *n*-$C_{10}H_{21}Br$	76 [b]	α-Se—CH: 4.40 (t, 6.0)
(3), R = R′ = CH_3	acetone + 2 C_6H_5SeH	80 [c]	see [4b]
(3), R—R′ = —$(CH_2)_5$—	cyclohexanone + 2 C_6H_5SeH	95 [d]	
(4), R = CH_3, R′ = H	*(1)*, R = CH_3, R′ = H, + $(C_6H_5S)_2$	60 [e]	CH_3: 1.67 (d, 7.0); CH: 4.48 (t, 7.0)
(4), R = R′ = CH_3	*(1)*, R = R′ = CH_3, + $(C_6H_5S)_2$	70 [f]	CH_3: 1.57 (s)
(5), R = CH_3, R′ = H, E = D	*(1)*, R = CH_3, R′ = H, + D_2O	>98	CH_3: 1.35 (broadened by D-coupling d, 7.0); α-Se—CHD: 2.72 (broadened by D-coupling q, 7.0)
(7), R = CH_3, R′ = H, R″—R‴ = —$(CH_2)_5$—	*(1)*, R = CH_3, R′ = H, + cyclohexanone	72 [g]	CH_3: 1.45 (d, 7.5); α-Se—CH: 3.24 (q, 7.5)
(7), R = CH_3, R′ = H, R″—R‴ = —$(CH_2)_7$—	*(1)*, R = CH_3, R′ = H, + cyclooctanone	65 [g]	CH_3: 1.50 (d, 7.0); α-Se—CH: 3.40 (q, 7.0)
(5), R = *n*-$C_{10}H_{21}$, R′ = H, E = H	*(1)*, R = *n*-$C_{10}H_{21}$, R′ = H, + H_2O	>95	α-Se—CH_2: 2.83 (t, 6.8)
(5), R = *n*-$C_{10}H_{21}$, R′ = H, E = D	*(1)*, R = *n*-$C_{10}H_{21}$, R′ = H, + D_2O	>95	α-Se—CHD: 2.84 (broadened by D-coupling t, 6.8)
(5), R = R′ = CH_3, E = D	*(1)*, R = R′ = CH_3, + D_2O	>98	$CD(CH_3)_2$: 1.37 (broadened by D-coupling s)
(7), R = R′ = CH_3, R″—R‴ = —$(CH_2)_5$—	*(1)*, R = R′ = CH_3, + cyclohexanone	85 [g]	CH_3: 1.35 (s)
(7), R—R′ = —$(CH_2)_5$—, R″ = *n*-C_5H_{11}, R‴ = H	*(1)*, R—R′ = —$(CH_2)_5$—, + hexanal	80 [g]	α-O—CH: 3.15 (m); terminal CH_3: 0.88 (deg. t)
(6), R = CH_3, R′ = H, E = D	*(2)*, R = CH_3, R′ = H, + D_2O	>98	α-S—CHD: 1.26 (broadened by D-coupling d, 7.0)
(8), R = CH_3, R′ = H, R″ = R‴ = C_6H_5	*(2)*, R = CH_3, R′ = H, + benzophenone	80	CH_3: 1.17 (d, 7.0); α-S—CH: 4.27 (q, 7.0)
(6), R = R′ = E = CH_3	*(2)*, R = R′ = CH_3, + CH_3I	40 [h]	$C(CH_3)_3$: 1.58 (s)
(8), R = R′ = CH_3, R″—R‴ = —$(CH_2)_5$—	*(2)*, R = R′ = CH_3, + cyclohexanone	95 [g]	CH_3: 1.18 (s)
(9a)	*(7)*, R—R′ = —$(CH_2)_5$—, R″ = *n*-C_5H_{11}, R‴ = H, + H_2O_2 in THF	65	vinylic H: 5.6 (m)
(10a)	*(7)*, R = R′ = CH_3, R″—R‴ = —$(CH_2)_5$—, + H_2O_2 in THF	95 [i]	CH_3: 1.75 (broadened by allyl-coupling s); vinylic H *cis* to CH_3: 4.70 (m); vinylic H *trans* to CH_3: 4.92 (m)

[a] B.p. 140–146 °C/0.1 torr. [b] B.p. 130 °C/0.02 torr. [c] B.p. 141–144 °C/0.08 torr.
[d] M.p. 76.5–77.5 °C. [e] B.p. 109 °C/0.02 torr. [f] B.p. 130 °C/0.3 torr.
[g] The alcohols were separated from $C_6H_5SeC_4H_9$ by chromatographic filtration over silica gel or by preparative TLC and isolated pure as oils.
[h] Separated by gas chromatography. [i] $n_D^{23} = 1.4822$ ([7]: $n_D^{26} = 1.4800$).

The modes of preparation, yields, and physical and NMR data of the compounds of types *(3)*–*(8)*, *(9a)*, and *(10a)* obtained are listed in Table 1.

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CAS Registry numbers: *(1)*, R = SeC_6H_5, R′ = H, 53198-49-5; *(1)*, R = CH_3, R′ = H, 53198-50-8; *(1)*, R = R′ = CH_3, 53230-01-6; *(1)*, R = *n*-$C_{10}H_{21}$, R′ = H, 53198-51-9; *(1)*, R—R′ = $(CH_2)_5$, 53198-52-0; *(2)*, R = CH_3, R′ = H, 53198-53-1; *(2)*, R = R′ = CH_3, 53198-54-2; *(3)*, R = CH_3, R′ = H, 26822-85-5; *(3)*, R = *n*-$C_{10}H_{21}$, R′ = H, 53198-55-3; *(3)*, R = R′ = CH_3, 35446-87-8; *(3)*, R—R′ = $(CH_2)_5$, 53198-56-4; *(4)*, R = CH_3, R′ = H, 53198-57-5; *(4)*, R = R′ = CH_3, 53198-58-6; *(5)*, R = CH_3, R′ = H, E = ^2H, 53198-59-7; *(5)*, R = *n*-$C_{10}H_{21}$, R′ = H, E = H, 53198-60-0; *(5)*, R = R′ = CH_3, E = ^2H, 53198-63-3; *(5)*, R = *n*-$C_{10}H_{21}$, R′ = H, E = ^2H, 53198-61-1; *(6)*, R = CH_3, R′ = H, E = ^2H, 53198-62-2; *(6)*, R = R′ = E = CH_3, 3019-19-0; *(7)*, R = CH_3, R′ = H, R″—R‴ = $(CH_2)_5$, 53198-64-4; *(7)*, R = CH_3, R′ = H, R″—R‴ = $(CH_2)_7$, 53198-65-5; *(7)*, R—R′ = $(CH_2)_5$, R″ = *n*-C_5H_{11}, R‴ = H, 53198-66-6; *(7)*, R = R′ = CH_3, R″—R‴ = $(CH_2)_5$, 53188-73-1; *(8)*, R = CH_3, R′ = H, R″ = R‴ = C_6H_5, 53198-67-7; *(8)*, R = R′ = CH_3, R″—R‴ = $(CH_2)_5$, 53198-68-8; *(9a)*, 53198-69-9; *(10a)*, 3908-31-4; CH_3I, 74-88-4; *n*-$C_{10}H_{21}Br$, 112-29-8; C_6H_5SeH, 645-96-5; $(C_6H_5S)_2$, 882-33-7; ^2H_2O, 7789-20-0; H_2O_2, 7722-84-1; Acetone, 67-64-1; Cyclohexanone, 108-94-1; Cyclooctanone, 502-49-8; Hexanal, 66-25-1; Benzophenone, 119-61-9

[1] *E. J. Corey* and *D. Seebach*, J. Org. Chem. *31*, 4097 (1966).

[2] a) *R. L. Sowerby* and *R. M. Coates*, J. Amer. Chem. Soc. *94* 4758 (1972); *I. Kuwajima*, *S. Sato*, and *Y. Kurata*, Tetrahedron Lett. *1972*, 737; b) *J. R. Shanklin*, *C. R. Johnson*, *J. Ollinger*, and *R. M. Coates*, J. Amer. Chem. Soc. *95*, 3429 (1973); c) *E. J. Corey* and *M. Jautelat*, Tetrahedron Lett. *1968*, 5787.

[3] *D. A. Shirley* and *B. J. Reeves*, J. Organometal. Chem. *16*, 1 (1969).

[4] a) *H. Gilman* and *R. L. Bebb*, J. Amer. Chem. Soc. *61*, 109 (1939); *H. Gilman* and *F. J. Webb*, *ibid. 71*, 4062 (1949); b) *D. Seebach* and *N. Peleties*, Angew. Chem. *81*, 465 (1969); Angew. Chem. internat. Edit. *8*, 450 (1969); Chem. Ber. *105*, 511 (1972).

[5] *D. N. Jones*, *D. Mundy*, and *R. D. Whitehouse*, Chem. Commun. *1970*, 86; *K. B. Sharpless* and *R. F. Lauer*, J. Amer. Chem. Soc. *95*, 2697 (1973).

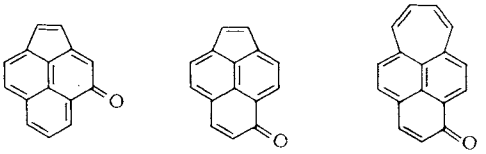
[6] *W. Dumont*, *P. Bayet*, and *A. Krief*, Angew. Chem. *86*, 308 (1974); Angew. Chem. internat. Edit. *13*, 274 (1974).

[7] *C. R. Johnson*, *C. J. Cheer*, and *D. J. Goldsmith*, J. Org. Chem. *24*, 3320 (1964).

Cyclohepta[*cd*]phenalen-6-one[1]

By *Ichiro Murata*, *Kagetoshi Yamamoto*, and *Yutaka Kayane*[*]

In connection with current interest in the peripheral conjugation in *peri*-condensed polyarenes, we have recently reported the synthesis and properties of the phenalenones *(1)*–*(3)*[2–4]. We have proposed that compounds *(1)* and *(2)* can be regarded as perturbed [13]-annulenones and compound *(3)* as a perturbed [15]-annulenone. In this communication we report the synthesis and properties of a further example of this type of compound, a novel tropone derivative, cyclohepta[*cd*]phenalen-6-one *(9)*.

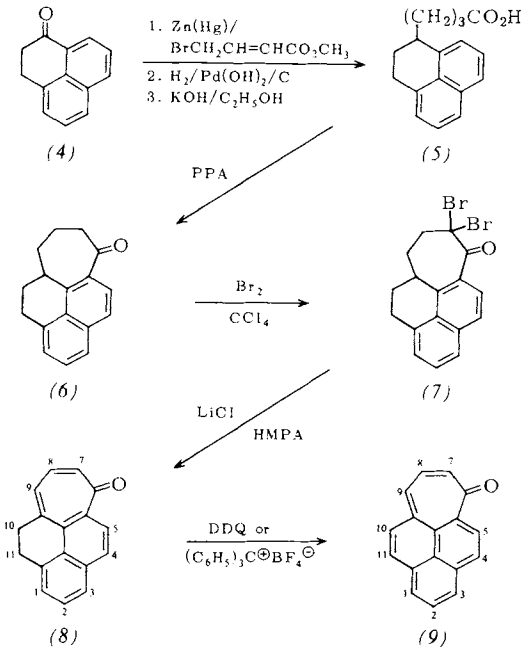


(1) *(2)* *(3)*

Reformatsky reaction of dihydrophenalenone *(4)*[5] with methyl 4-bromocrotonate afforded the hydroxy ester, which, on hydrogenation with palladium hydroxide on charcoal followed by hydrolysis with potassium hydroxide in ethanol gave the carboxylic acid *(5)*[6], m.p. = 90 °C, in 48% yield [referred to *(4)*]. Cyclization of *(5)* with polyphosphoric acid (PPA) at 90 °C for 1 h afforded the tetracyclic ketone *(6)*[6] in 75% yield: m.p. = 97.5–98 °C; IR (KBr): 1665 cm^{-1}; ^1H-NMR ($CDCl_3$): δ = 1.6–2.2 (m, 6H), 2.5–2.7 (m, 2H), 2.9–3.5 (m, 3H) and 7.0–7.7 (m, 5H). The ketone *(6)* was converted by treatment with bromine in dry carbon tetrachloride into the α,α-dibromoketone *(7)* in quantitative yield: viscous oil; IR (neat): 1695 cm^{-1}; ^1H-NMR: δ = 1.5–2.7 (m,

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6H), 2.8—3.3 (m, 3H) and 7.0—7.7 (m, 5H). Dehydrobromination of *(7)* to give the tropone *(8)*[6] (in 66% yield) was accomplished by heating in hexamethylphosphoric triamide (HMPA) with LiCl for 1 h at 95—100°C; *(8)*: yellow plates, m.p. = 90.0—90.5°C; *m/e* = 232 (M^+, 64%), 204 ($M^+ - CO$, 100%), 203 (93%) and 202 (pyrene ion, 82%); IR (KBr): 1625, 1590, 1580 cm^{-1}. The absorption bands of the UV spectrum of



(4) *(5)* *(6)* *(7)* *(8)* *(9)*

(8) (λ_{max} (ethanol) = 243 ($\log\varepsilon = 4.38$), 287 (4.33) and 344 nm (3.91)] are in good agreement with those of cyclohepta[*a*]naphthalen-7-one[7].

The conversion of *(8)* into the desired fully conjugated ketone *(9)*[6] was effected by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in benzene solution in a sealed tube at 120°C for 20 h (yield 21%). The compound *(9)* was found to be more readily accessible by treatment of *(8)* with triphenylmethyl tetrafluoroborate in refluxing acetic acid under nitrogen for 2 h (33% yield): orange scales, m.p. = 144—146°C; *m/e* = 230 (M^+, 27%) and 202 ($M^+ - CO$, 100%); IR (KBr): 1600, 1590 and 1560 cm^{-1}; UV: λ_{max} (ethanol) = 249 ($\log\varepsilon = 4.48$), 311 (4.07), 321 (4.08) and 430 nm (4.23); λ_{max} (cyclohexane) = 246 (4.47), 311 (4.10) and 430 nm (4.19).

Table 1. 100-MHz-^{1}H-NMR data of *(8)* and *(9)* (δ values; TMS internal).

	in $CDCl_3$		in CF_3COOH	
	(8)	*(9)*	*(8)*	*(9)*
H-1,2,3	7.30—7.78	7.68—8.02	7.82—8.21	8.63—9.16
H-7,8,9	6.73—7.10	7.20—7.56	8.24—8.62	
H-10,11	2.88—3.35		3.48—3.82	
H-4	7.96	8.18	8.62	9.23
H-5	8.24	8.77	9.05	9.74
$J_{4,5}$	9.0 Hz	9.0 Hz	9.2 Hz	9.2 Hz

The NMR chemical shifts and coupling constants of *(8)* and *(9)* are summarized in Table 1. It is apparent that in the transition from the dihydroketone *(8)* to the fully conjugated ketone *(9)*, all the vinyl protons move downfield by 0.22 to 0.53 ppm. The most plausible explanation suggests that these downfield shifts arise from deshielding due to the existence of a diamagnetic ring current induced in the periphery of *(9)*. The diatropic effect is enhanced when *(9)* is protonated. Differences in the chemical shifts between the neutral and protonated species of *(9)* are even larger than those observed in the case of *(8)*; this also underlines the significance of the peripheral conjugation in *(9)*.

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CAS Registry numbers: *(4)*, 518-85-4; *(5)*, 53260-24-5; *(6)*, 53260-25-6; *(7)*, 53260-26-7; *(8)*, 53260-27-8; *(9)*, 53260-28-9; Methyl 4-bromocrotonate, 1117-71-1; Bromine, 7726-95-6

[1] The Chemistry of the Phenalenium System, Part 18.—Part 17: *I. Murata, K. Yamamoto*, and *O. Hara*, Tetrahedron Lett. *1974*, 2047.

[2] *I. Murata* and *K. Yamamoto*, Chem. Lett. *1973*, 413.

[3] *I. Murata, K. Yamamoto, T. Hirotsu*, and *M. Morioka*, Tetrahedron Lett. *1972*, 331.

[4] *I. Murata, K. Yamamoto*, and *T. Hirotsu*, Tetrahedron Lett. *1972*, 3389.

[5] *L. F. Fieser* and *M. D. Gates*, J. Amer. Chem. Soc. *62*, 2335 (1940); *V. Boekelheide* and *C. E. Larrabee*, *ibid. 72*, 1240 (1950); *D. M. Reid* and *R. G. Sutherland*, J. Chem. Soc. *1963*, 3295.

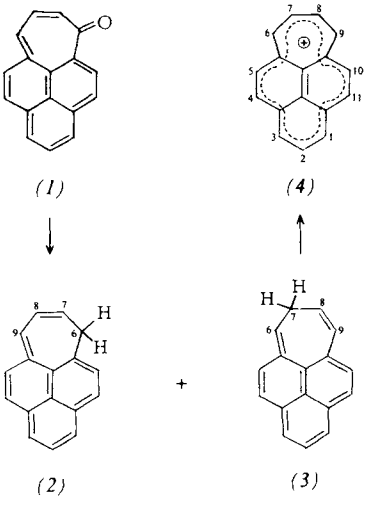
[6] All new compounds described in this paper gave satisfactory elemental analytical data.

[7] *S. Julia* and *Y. Bonnet*, Bull. Soc. Chim. Fr. *1957*, 1340.

The Cyclohepta[*cd*]phenalenium Ion[**]

By *Ichiro Murata, Kagetoshi Yamamoto*, and *Yutaka Kayane*[*]

Although there has been considerable interest in the neutral nonalternant isomers of pyrene, the ionic 14π perimeter species which are isoelectronic with pyrene have received little attention. According to theoretical predictions by *Zahradnik*[2] the cyclohepta[*cd*]phenalenium ion *(4)* ought to be quite stable.



(1) *(4)* *(2)* *(3)*

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[**] The Chemistry of the Phenalenium System, Part 19.—Part 18: [1].

Here we describe the synthesis of *(4)* as the first example of a 14π perimeter cationic system.

Reduction of cyclohepta[*cd*]phenalen-6-one *(1)*[1] with $LiAlH_4$—$AlCl_3$ complex in ether at −50 °C for 2 h led to a mixture of isomeric hydrocarbons, 6*H*- *(2)* and 7*H*-cyclohepta[*cd*]phenalene *(3)* (in a ratio of about 9 : 13). The mixture was isolated in 56% yield after chromatography (hexane) on alumina deactivated with 10% water. All manipulations during the reaction and work-up have to be carried out under nitrogen in order to avoid decomposition of the products. Although compounds *(2)* and *(3)* could not be separated due to their pronounced sensitivity toward air and heat, their structural assignments were readily borne out by 100-MHz ^{1}H-NMR and double resonance experiments. The mixture showed signals for *(2)* at δ = 2.71 (2H-6, d, $J_{6,7}$ = 6.7 Hz), 5.51 (H-7, dt, $J_{7,6}$ = 6.7, $J_{7,8}$ = 9.2 Hz), 6.33 (H-8, dd, $J_{8,7}$ = 9.2, $J_{8,9}$ = 6.5 Hz), 6.84 (H-9, d, $J_{9,8}$ = 6.5 Hz), and for *(3)* at δ = 1.66 (2H-7, dd, $J_{7,6}$ = 7.3, $J_{7,8}$ = 6.5 Hz), 4.82 (H-8, dtd, $J_{8,7}$ = 6.5, $J_{8,9}$ = 8.5, $J_{8,6}$ = 2.4 Hz), 5.27 (H-6, td, $J_{6,7}$ = 7.3, $J_{6,8}$ = 2.4 Hz), and 6.66 (H-9, d, $J_{9,8}$ = 8.5 Hz) along with signals for the aromatic protons at 7.02—8.07 ppm. Irradiation at δ = 2.71 [H-6 of *(2)*] simplified the multiplet at δ = 5.51 attributed to H-7 of *(2)* into a clean doublet with J = 9.2 Hz. Another irradiation at δ = 1.66 [H-7 of *(3)*] changed the multiplets at δ = 5.27 and δ = 4.82 into a broad singlet and a broad doublet, respectively. The mass spectrum of a mixture of *(2)* and *(3)* exhibits peaks at *m/e* = 216 (M^+, 100%), 215 ($M^+ - H$, 73%) and 202 (pyrene ion, 21%).

Hydride abstraction from the freshly prepared mixture of *(2)* and *(3)* with triphenylmethyl tetrafluoroborate in chloroform at room temperature gave the desired cation *(4)*[3] in 79% yield [reddish brown crystals, which sinter at 199—201 °C and show no definite m.p.; IR (KBr): 1040 cm^{-1} (strong, broad, BF_4^-); UV (acetonitrile): λ_{max} = 224 (log ε = 4.40), 257 (3.99), 291 (4.37), 307 (4.37, sh), 316 (4.40), 334 (4.18, sh) and 475 nm (4.49)][4]. The 100-MHz ^{1}H-NMR spectrum of *(1)* in CF_3COOD consists of superimposed signals of AA'XX', 2AB and A_2B spin systems at δ = 9.08 (H-7,8 or H-6,9), 9.66 (H-6,9 or H-7,8), 9.16 (H-5,10)[5], 9.50 (H-4,11)[5], 9.40 (H-1,3) and 9.00 (H-2) with coupling constants of $J_{6,7} = J_{8,9}$ = 10.9, $J_{7,8}$ = 9.0, $J_{6,8} = J_{7,9}$ = 1.4, $J_{6,9}$ = 0, $J_{4,5} = J_{10,11}$ = 8.9 and $J_{1,2} = J_{2,3}$ = 7.7 Hz. Both the appreciable downfield chemical shift with rather narrow range (δ = 9.00—9.66 ppm) and the symmetrical pattern of the signals show the species to have fully delocalized structure with C_{2v}-symmetry.

Despite the fact that a unit positive charge resides over the fifteen peripheral carbon atoms, the ^{1}H-NMR signals of *(4)* are comparable to those of the tropylium ion (δ = 9.20 in CH_3CN)[6] and of the phenalenium ion (δ = 9.30 and 8.48 in $AsCl_3$)[7]. This proves the existence of a strong induced diamagnetic ring current associated with the 14π perimeter of *(4)*. These findings suggest that the ion *(4)* can be regarded as a perturbed [15]annulenium ion weakly coupled with a localized central vinyl crosslink.

In accord with theoretical prediction[2], the ion *(4)* is extremely stable. *(4)* (as tetrafluoroborate) can be stored without any change under atmospheric conditions. Furthermore, *(4)* shows essentially the same UV spectrum in water as in acetonitrile. The pK_{R^+} value of *(4)* was found to be ≥ 8.4[8]; this is about 1pK unit larger than of the 8-cycloheptatrienylheptafulvenyl cation (pK_{R^+} = 7.1[9], 7.49[10]). To our knowledge, *(4)* is the most stable hydrocarbon cation so far reported.

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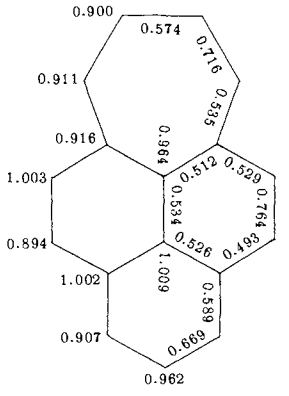
CAS Registry numbers: *(1)*, 53260-28-9; *(2)*, 53260-41-6; *(3)*, 53260-42-7; *(4)*, 53260-31-4; *(4)*BF_4, 53260-32-5; Triphenylmethyl tetrafluoroborate, 341-02-6

[1] *I. Murata, K. Yamamoto*, and *Y. Kayane*, Angew. Chem. *86*, 861 (1974); Angew. Chem. internat. Edit. *13*, 807 (1974).

[2] *R. Zahradnik, J. Michl*, and *J. Pancir*, Tetrahedron *22*, 1355 (1966).

[3] Satisfactory C, H analytical values were obtained for *(4)*.

[4] Prof. *Zahradnik* has kindly put at our disposal the following PPP LCI-SCF results (π-electron densities, π-bond orders and electronic spectrum) for



(4)

(4): λ_{max} = 433, 386, 355, 306, 281, 264, 249 nm. We thank Prof. *R. Zahradnik* and Dr. *Z. Slanina* for the calculations.

[5] The assignment of H-5,10 and H-4,11 was made according to the calculated π-electron density at their respective carbon atoms [4].

[6] *G. Fraenkel, R. E. Carter, A. McLachlan*, and *J. H. Richards*, J. Amer. Chem. Soc. *82*, 5846 (1960); *T. Schaeffer* and *W. G. Schneider*, Can. J. Chem. *41*, 966 (1963); *J. R. Leto, F. A. Cotton*, and *J. S. Waugh*, Nature *180*, 978 (1957).

[7] *H. Prinzbach, V. Freudenberger*, and *U. Scheidegger*, Helv. Chim. Acta, *50*, 1087 (1967).

[8] Standard spectrophotometric methods were used for the pK_{R^+} determination in 20% aqueous acetonitrile solution. Each absorbance of 475 nm at various pH values was measured 90 s after preparation of the solution. The pK_{R^+} value of 8.4 thus obtained is the lower limit, since the intensity of absorbance decreases with elapse of time in the pH range near pK_{R^+}. Thus, the measurement at 180 s after preparation of the solution yields a somewhat small value of 8.1 for the pK_{R^+} of *(4)*.

[9] *I. Fleming*, J. Chem. Soc. Perkin I, *1973*, 1019.

[10] *Y. Kayama, M. Oda*, and *Y. Kitahara*, Chem. Lett. *1973*, 1169.

Synthesis of Pyrimidines from 2,*N*-Dialkylcyanoacetamides[1]

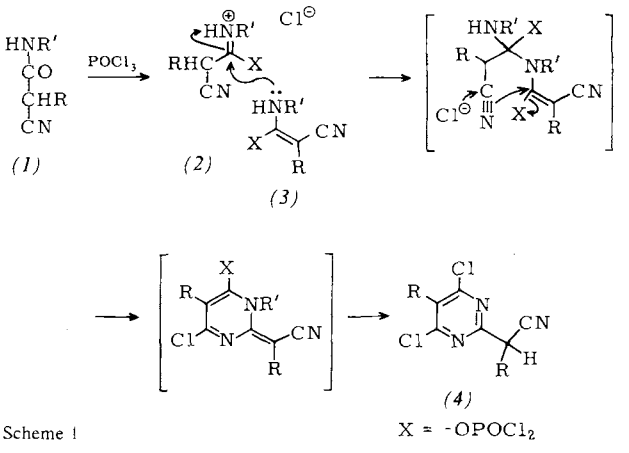
By *A. L. Cossey, R. L. N. Harris, J. L. Huppatz*, and *J. N. Phillips*[*]

We have previously reported on novel syntheses of pyridines and pyridinium salts from variously substituted cyanoacetamides[2]. We now describe a further extension of this reaction to the synthesis of pyrimidine derivatives.

When 2-cyano-*N*-methylpropionamide *(1a)* was heated with phosphorus oxide trichloride at 100 °C for 16 h a product was isolated to which the structure *(4a)* was assigned on the basis of the following findings: microanalysis and high resolution mass spectral data indicated the formula $C_8H_7N_3Cl_2$; the IR band at 2258 cm^{-1} is consistent with an unconjugated nitrile, and the NMR spectrum (D_6-DMSO) showed signals at δ = 2.43 (s, 1 ring CH_3), 1.65 (d, 1 side chain CH_3, J = 3.5 Hz), and 4.6 (q, 1 methine H, J = 3.5 Hz). On deuteration the methine proton exchanged, and the signal due to the adjacent methyl group collapsed to a singlet at

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$\delta = 1.7$. Furthermore, when *N*-ethyl-2-cyanopropionamide *(1b)* was similarly treated, the product was identical to that described above, confirming that one alkylamino group and an *N*-alkyl group were lost during the self-condensation.



Scheme 1

We believe that the pyrimidine derivatives *(4)* are formed *via* the route shown in Scheme 1 (cf. Ref. [2]) in which the key step is the formation of a C—N bond in the condensation of the salt *(2)* with its corresponding base *(3)*.

(For further examples of this reaction see Table 1.)

Table 1. Pyrimidines *(4)* from the reaction of 2,*N*-dialkylcyanoacetamides *(1)* and $POCl_3$ [3].

Educt	R	R'	Product	Yield [%]	M.p. [°C]
(1a)	CH_3	CH_3	*(4a)*	26	83—84
(1b)	CH_3	C_2H_5	*(4a)*	23	83—84
(1c)	C_2H_5	CH_3	*(4b)*	37	39—40
(1d)	C_2H_5	C_2H_5	*(4b)*	40	39—40
(1e)	i-C_3H_7	CH_3	*(4c)*	44	43—45

2-(4,6-Dichloro-5-methylpyrimidinyl)propionitrile (4a)

(1a) (5.6 g, 0.05 mol) and $POCl_3$ (16 g, 0.11 mol) are heated on a steam bath under reflux in absence of moisture for 16 h. The reaction mixture is then cooled, cautiously poured into icewater and rendered alkaline with 20% NaOH. The crude product is extracted into chloroform (3 × 50 ml) and the combined extracts washed and dried over Na_2SO_4. The solvent is removed and the residue chromatographed on a silica gel column (30 × 4 cm). Elution with chloroform/petroleum ether (b. p. 40—60 °C (2:1)) affords *(4a)* as a colorless oil (1.4 g, 26%), which solidifies and can be crystallized from ethanol as colorless prisms (m.p. 83—84 °C).

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CAS Registry numbers: *(1a)*, 53260-43-8; *(1b)*, 53260-44-9; *(1c)*, 53260-45-0; *(1d)*, 53260-46-1; *(1e)*, 53260-47-2; *(4a)*, 53260-48-3; *(4b)*, 53260-49-4; *(4c)*, 53260-50-7; $POCl_3$, 10025-87-3

[1] Amide-Acid Chloride Adducts in Organic Synthesis, Part 4.—Part 3: [3].

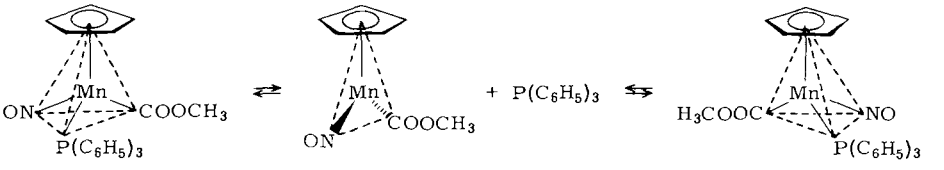
[2] a) *A. L. Cossey, R. L. N. Harris, J. L. Huppatz*, and *J. N. Phillips*, Angew. Chem. *84*, 1183 (1972); Angew. Chem. internat. Edit. *11*, 1098 (1972); b) *A. L. Cossey, R. L. N. Harris, J. L. Huppatz* and *J. N. Phillips*, Angew. Chem. *84*, 1185 (1972); Angew. Chem. internat. Edit. *11*, 1100 (1972); c) *A. L. Cossey, R. L. N. Harris, J. L. Huppatz*, and *J. N. Phillips*, Angew. Chem. *84*, 1184 (1972); Angew. Chem. internat. Edit. *11*, 1099 (1972).

[3] The structures of all compounds reported are consistent with analytical, NMR and mass spectral data.

Evidence for a Chiral Intermediate on Phosphane Substitution in the Complex $(+)$-$C_5H_5Mn(NO)(COC_6H_5)P(C_6H_5)_3$[1]

By *Henri Brunner, Jean Aclasis, Manfred Langer*, and *Wolfgang Steger*[*]

Racemization of the species (+)- and (−)-$C_5H_5Mn(NO)(COOCH_3)P(C_6H_5)_3$ in benzene or tetrahydrofuran solution is a first order reaction with respect to the complex concentration; it is independent of the concentration of added triphenylphosphane[2]. In the presence of $P(C_6D_5)_3$ the deuterated triphenylphosphane is incorporated into the complex[3], the rate constants for racemization and phosphane exchange proving to be identical. These findings are consonant with the simple dissociative racemization mechanism (1) whose rate-determining step is cleavage of the Mn—P bond[2, 3].



(1)

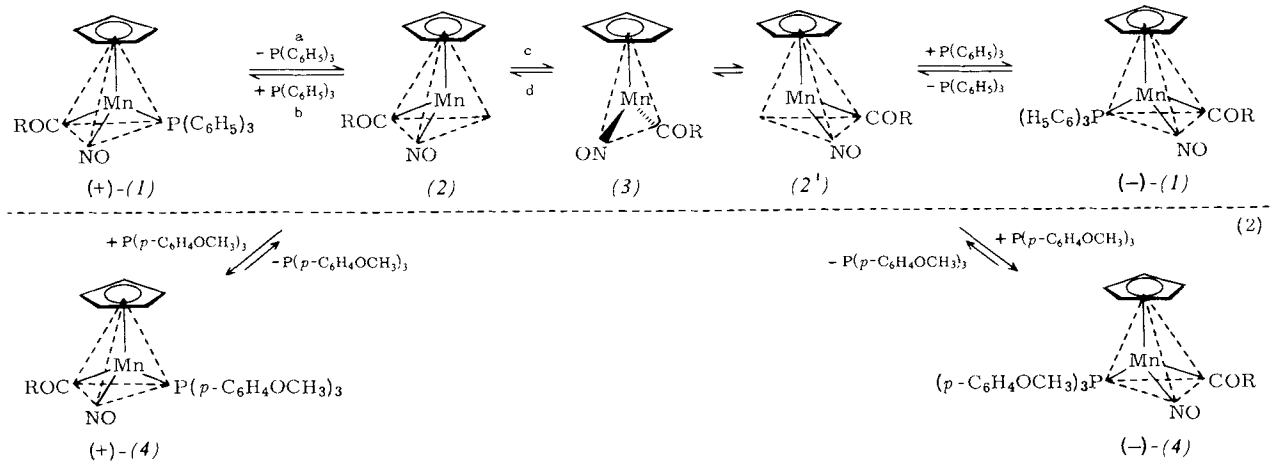
The newly found benzoyl complex (+)-$C_5H_5Mn(NO)(COC_6H_5)P(C_6H_5)_3$ (+)-*(1)* also undergoes first order racemization in solution. In contrast to the ester (+)-$C_5H_5Mn(NO)(COOCH_3)P(C_6H_5)_3$, however, this racemization is concentration dependent; it proceeds slightly faster in dilute solution than in concentrated solution. Moreover, the racemization of (+)-*(1)* is retarded by addition of $P(C_6H_5)_3$ (Table 1). Since the phosphane concentration does not change during polarimetric measurement the change in rotation with time can be evaluated according to first order kinetics for each addition of phosphane.

This dependence upon concentration and triphenylphosphane can be interpreted by an extension of the simple dissociation mechanism (1) [cf. (2)].

The three-coordinate chiral intermediate *(2)* arising on dissociation of (+)-*(1)* (reaction step a) can either revert to (+)-*(1)* with retention of configuration in the presence of $P(C_6H_5)_3$ (step b) or achieve planarity with loss of chirality (step c). Promotion of reaction b compared to c explains the retardation of racemization at higher concentrations and on addition of $P(C_6H_5)_3$.

It remains to be established whether *(3)* is an intermediate or a transition state. Assumption of the chiral intermediates *(2)* and *(2')*, on the other hand, is supported by kinetic and stereochemical arguments. Similar intermediates have been postulated in the reaction of $C_5H_5Fe(CO)_2R$ with nucleophiles L[5].

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(2)

Applying the Bodenstein steady state concept to Scheme 2 and appropriate simplification affords the expression

$$\frac{k_c}{k_b} = \frac{k_{with} \times [P(C_6H_5)_3]}{k_{without} - k_{with}}$$

where k_b and k_c are the rate constants for steps b and c in (2) and k_{with} and $k_{without}$ are the rate constants for racemization of (+)-(1) with and without addition of $P(C_6H_5)_3$. Table 1 reveals that the competition constant k_c/k_b remains constant on variation of the complex to triphenylphosphane concentration ratio from 1:1 to 1:20. Hence the observed $P(C_6H_5)_3$ dependence of racemization is also quantitatively compatible with Scheme (2).

Table 1. Racemization of (+)-(1) in toluene, $c = 3.86 \times 10^{-3}$ mol/l, at 25 °C with addition of $P(C_6H_5)_3$ in the molar ratio 1:x.

x	$\tau_{1/2}$ [min]	$k_{with} \times 10^4$ [s^{-1}]	$k_c/k_b \times 10^2$ [mol/l]
1	22.1	5.23	7.5
2	23.7	4.87	6.0
3	25.2	4.58	5.8
4	26.5	4.36	5.9
5	28.0	4.13	5.8
6	29.0	3.98	6.1
7	30.6	3.78	5.9
8	32.0	3.61	5.9
10	34.5	3.35	6.0
20	45.0	2.57	6.8
0	21.0	$k_{without} = 5.50 \times 10^{-4}$ [s^{-1}]	

In solutions of (1) the triphenylphosphane ligand can be replaced by tri-*p*-anisylphosphane. Optically active (4) ($\tau_{1/2}$ 337 min, toluene, 20 °C) racemizes much more slowly than optically active (1) ($\tau_{1/2}$ 50 min, toluene, 20 °C).

If racemization of (+)-(1) ($[\alpha]_{546}^{25}$ +255°; $[\alpha]_{436}^{25}$ −1680°; 2 mg/ml toluene) is performed in toluene at 20 °C in the presence of a fivefold excess of tri-*p*-anisylphosphane and interrupted after 50 min, chromatography of the reaction mixture over SiO_2 at −25 °C affords approximately equal amounts of unchanged (+)-(1) ($[\alpha]_{546}^{25}$ +210°; $[\alpha]_{436}^{25}$ −1620°) as the first zone (toluene/ether 10:1) and the optically active substitution product (+)-(4) ($[\alpha]_{546}^{25}$ +130°; $[\alpha]_{436}^{25}$ −815°) as the second zone (toluene/ether 5:1). The latter compound is ascribed the same configuration as (+)-(1) on the basis of its chiroptical properties.

Thus according to Scheme (2) substitution of triphenylphosphane by other ligands with retention of configuration is possible, although the mechanism is dissociative. Racemization of the esters (+)- and (−)-$C_5H_5Mn(NO)(COOCH_3)P(C_6H_5)_3$ probably also follows mechanism (2) even though the chiral intermediates defy detection in this case owing to the far greater competition constant. Formation of a chiral intermediate on dissociation of (+)-(1) appears significant with regard to the stereochemistry, rearrangement, and reactions of photochemically generated carbonylmetal fragments[4].

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CAS Registry numbers:
(+)-(1), 53402-92-9; (+)-(4), 53352-73-1

[1] Optically Active Transition Metal Complexes, Part 28. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. Part 27: *H. Brunner* and *W. Rambold*, Z. Naturforsch. *29b*, 367 (1974).

[2] *H. Brunner* and *H.-D. Schindler*, Chem. Ber. *104*, 2467 (1971).

[3] *H. Brunner* and *H.-D. Schindler*, Z. Naturforsch. *26b*, 1220 (1971).

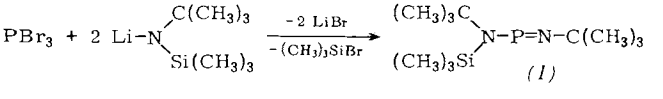
[4] *M. Wrighton*, Chem. Rev. *74*, 401 (1974).

[5] *K. Nicholas*, *S. Raghu*, and *M. Rosenblum*, J. Organometal. Chem. *78*, 133 (1974).

Trimethylsilyl(*tert*-butyl)amino(*tert*-butyl)iminothiophosphorane—A Derivative of Monomeric Metathiophosphoric Acid

By *Otto J. Scherer* and *Norbert Kuhn*[*]

Attempts to isolate the λ^5-phosphorus compounds having coordination number 3 (*e.g.* metaphosphoric acid derivatives) which have repeatedly been postulated[1] as intermediates have so far only succeeded in a single case, that of a completely *N*-silylated aminobis(imino)phosphorane[2]. It has now been found that P^{III} and P^{V} having the unusual coordination number 2 and 3, respectively, are apparently stabilized to an even greater extent by *N*-*tert*-butyl groups than by *N*-trimethylsilyl groups.



(1)

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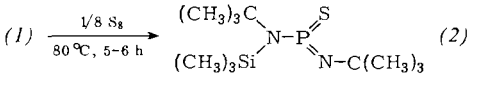
Reaction of phosphorus tribromide with lithium (*tert*-butyl)-(trimethylsilyl)amide in the molar ratio 1:2 furnishes a *ca.* 30% yield of trimethylsilyl(*tert*-butyl)amino(*tert*-butyl)iminophosphane *(1)*.

Compound *(1)* is a distillable yellowish green liquid, m.p. 17—19 °C. In its stability, the compound differs considerably from the trisilylated analog[2], the only known phospha(III)azene[3]. Whereas the latter reacts already at room temperature with carbon tetrachloride, trimethylsilyl azide, or sulfur[4], *(1)* requires elevated temperatures for such reactions[5]. A solution of *(1)* undergoes *ca.* 10% decomposition on exposure to air (open NMR sample tube) for 20 h; the analogous persilylated compound undergoes quantitative conversion within *ca.* 2 h. Hydrolysis of *(1)* in the presence of oxygen affords good yields of $[(CH_3)_3CNH]_2P(O)—O—P(O)[HNC(CH_3)_3]_2$, a diphosphoric tetraamide.

^{1}H-NMR spectrum (10% solution in C_6H_6; TMS internal; 37 °C): $\delta CH_3Si = -0.43$ ppm (d), $^4J_{PH} = 0.5$ Hz; $\delta CH_3C = -1.38$ ppm (d), $^4J_{PH} = 2.1$ Hz. The temperature dependence of the spectrum (at −30 °C: $\delta(CH_3)_3C$ = doublet; $^4J_{PH} = 1.9$ and 2.4 Hz, $\Delta\nu = 6.0$ Hz; coalescence temperature = 0 °C; $\Delta G_c^{\ddagger} = 14.5$ kcal/mol[6]) reveals that the $(CH_3)_3Si$ group fluctuates at room temperature[7].—^{31}P-NMR spectrum (20% solution in C_6H_{12}; H_3PO_4 external): $\delta = -327.5$ ppm (greatest downfield shift yet observed[8]).

UV spectrum[9] (*n*-heptane): $\lambda_{max} = 278$ (log ε = 3.40, probably $\pi\rightarrow\pi^*$ transition), 345 nm (2.00, probably $n\rightarrow\pi^*$ transition). Mass spectrum (20 eV): *m/e* = 246 (21%, M^+), 231 (8), 190 (100), 175 (26), 135 (26), 73 (9), 57 (5).

Compound *(1)* is oxidized by sulfur at 80 °C in *ca.* 80% yield to trimethylsilyl(*tert*-butyl)amino(*tert*-butyl)iminothiophosphorane *(2)*, the first isolable monomeric metathiophosphoric acid derivative.



Compound *(2)* is a distillable yellowish green liquid, m.p. 1—3 °C, which is stable to at least 100 °C. At room temperature, no exchange of the $(CH_3)_3Si$ group is observed in the ^{1}H-NMR spectrum (10% solution in CCl_4, TMS internal): $\delta CH_3Si = -0.45$ ppm (s); $\delta CH_3C(N=) = -1.35$ ppm (d), $^4J_{PH} = 1.5$ Hz; $\delta CH_3CN(Si) = -1.57$ ppm (s).—^{31}P-NMR spectrum (30% solution in C_6H_{12}; H_3PO_4 external): $\delta = -136.0$ ppm.—Mass spectrum (22 eV): *m/e* = 278 (5%, M^+), 263 (41), 246 (47), 223 (25), 207 (100), 190 (16), 73 (33), 57 (19). Unlike *(1)*, compound *(2)*, which readily dissolves in aprotic organic solvents, is extremely sensitive to hydrolysis.

Experimental:

(1): A solution of $(CH_3)_3CNHSi(CH_3)_3$ (22.2 g, 153.1 mmol) in ether (100 ml) is metalated with a *n*-C_4H_9Li/hexane solution (92 ml, 153.1 mmol) and refluxed for 2 h. The resulting solution is added dropwise over 2 h to a solution of PBr_3[10] (20.7 g, 76.5 mmol) in ether (250 ml) at −78 °C, the reaction mixture stirred for *ca.* 12 h and evaporated down in a water pump vacuum. The product is taken up in pentane (30 ml) and filtered through a G3 frit. Fractional distillation (b.p. 60—90 °C/0.2 torr; bath temperature up to 130 °C) and redistillation (Vigreux column) affords *(1)* (b.p. 38—40 °C/0.1 torr; yield 6.0 g, 32%).

(2): A solution of *(1)* (3.5 g, 14.2 mmol) in benzene (15 ml) is refluxed with sulfur (480 mg, 15 mmol) for 5—6 h. Fractional distillation furnishes *(2)* (b.p. 56—58 °C/0.01 torr; yield 3.1 g, 78%).

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supplemented: July 15, 1974 [Z 102 IE]
German version: Angew. Chem. *86*, 899 (1974)

[1] *O. J. Scherer, P. Klusmann,* and *N. Kuhn,* Chem. Ber. *107*, 552 (1974); *J. Wiseman* and *F. H. Westheimer,* J. Amer. Chem. Soc. *96*, 4262 (1974); *R. Breslow, A. Feiring,* and *F. Hermann, ibid. 96*, 5937 (1974); and references cited (cf. also ref. [2]).

[2] *O. J. Scherer* and *N. Kuhn,* Chem. Ber. *107*, 2123 (1974); *E. Niecke* and *W. Flick,* Angew. Chem. *86*, 128 (1974); Angew. Chem. internat. Edit. *13*, 134 (1974).

[3] By analogy with common terminology [*H. R. Allcock:* Phosphorus-Nitrogen Compounds. Academic Press, New York 1972, p. 7; *S. Pantel* and *M. Becke-Goehring:* Sechs- und achtgliedrige Ringsysteme der Phosphor-Stickstoff-Chemie. Springer, Berlin 1969, p. 1] we propose the name phospha(III)azenes for compounds of type $-P=N-$; as a consequence the designation "phosphazenes" for λ^5-phosphorus compounds has to be expanded to phospha(V)azenes.

[4] No compound analogous to *(2)* has yet been isolated.

[5] Reaction of *(1)* with CCl_4 or $(CH_3)_3SiN_3$ yields a product mixture; *O. J. Scherer* and *N. Kuhn,* to be published.

[6] This value is to be refined by line shape analysis. At concentrations >10%, the concentration dependence of the coalescence temperature indicates that, apart from the intramolecular shift of the $(CH_3)_3Si$ group occurring at high dilution (<10%), an intermolecular process also comes into play.

[7] Cf. *O. J. Scherer,* Angew. Chem. *81*, 871 (1969); Angew. Chem. internat. Edit. *8*, 861 (1969); *O. J. Scherer* and *R. Thalacker,* Z. Naturforsch. *27b*, 1429 (1972); *E. Niecke* and *W. Flick,* Angew. Chem. *85*, 586 (1973); Angew. Chem. internat. Edit. *12*, 585 (1973).

[8] *M. M. Crutchfield, C. H. Dungan, L. H. Letcher, V. Mark,* and *J. R. Van Wazer,* Top. Phosphorus Chem. *5*, 236 (1967); *G. Mavel* in *E. F. Mooney:* Annual Reports in NMR Spectroscopy. Academic Press, Vol. 5B, 95 (1973).

[9] Compound *(1)*, which can formally be regarded as a triazene derivative in which one N atom is replaced by P, differs markedly in color from comparable colorless $(CH_3)_3Si(CH_3)N—N=N—CH_3$: *F. E. Brinckman, H. S. Haiss,* and *R. A. Robb,* Inorg. Chem. *4*, 936 (1965).

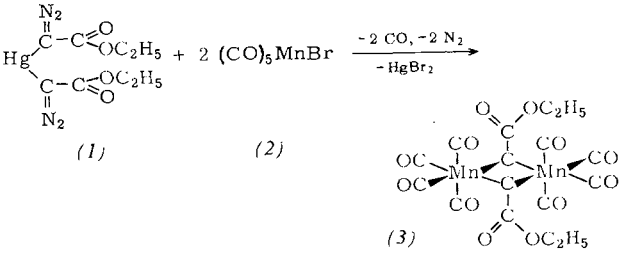
[10] On use of equimolar amounts of PCl_3, *(1)* is formed in *ca.* 20% yield.

Pentacarbonylmanganese Bromide—An Organometallic Trapping Reagent for Ethoxycarbonylcarbyne[1]

By *Wolfgang Anton Herrmann*[*]

On UV photolysis in cyclohexene, bis(ethoxycarbonyldiazomethyl)mercury *(1)* affords products whose formation can be attributed to the intermediacy of ethoxycarbonylcarbyne (ethoxycarbonylmethylidine)[2]. We have now been able to trap this extremely reactive intermediate directly for the first time.

If the diazo compound *(1)* is allowed to react with pentacarbonylmanganese bromide *(2)* in the molar ratio 1:2, work-up of the crude product by column chromatography yields a pale yellow readily crystallizing neutral compound which is stable up to about 130 °C; total elemental analysis and osmometric molecular weight determination indicate the composi-



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tion $C_{16}H_{10}O_{12}Mn_2$. On the basis of analytical data and the following arguments the new complex is assigned the structure *(3)* in which two tetracarbonylmanganese fragments are symmetrically bridged by two ethoxycarbonylcarbyne ligands.

1) In the ^{1}H-NMR spectrum (60 MHz; 33 °C) the methylene protons appear as a quartet at $\tau = 5.64$, the methyl protons as a triplet at $\tau = 8.65$ in the intensity ratio 2:3 (CD_2Cl_2; internal TMS). No hindrance to free rotation of the ester groups about the C—C axes can be observed in the ^{1}H-NMR spectrum down to −70 °C.

2) In the mass spectrum (70 eV; direct sample injection at 120 °C; $T_0 = 40$—60 °C) the molecular ion M (*m/e* = 504) is accompanied, *inter alia*, by the complete fragmentation sequence $M - nCO$ ($n = 1$ to 8). Hence *(3)* contains eight carbonyl groups bound to the metal.

3) In accord with group-theoretical predictions for a molecule of point group D_{2h}, the IR spectrum (*n*-hexane) contains four bands in the range of the ν_{CO} fundamental vibration (B_{3u}(a), 2076 m; B_{1u}, 2004 vs; B_{3u}(b), 1993 w-s; B_{2u}, 1956 cm^{-1} vs) whose positions and intensities resemble those of the IR absorptions of the isostructural complexes $[(CO)_4MX]_2$ (M = Mn, Tc, Re; X = Cl, Br, I)[3].

4) The numbers of calculated and observed Raman active ν_{CO} fundamental vibrations agree: The four emission bands (B_{2g}, 2090 vs; B_{1g}, 1999 vs; A_g(a), 1954 m; A_g(b), 1935 cm^{-1} m) are not coincident with the IR absorptions owing to the selection rule applicable to *(3)* owing to centrosymmetry.

5) The highly symmetric charge distribution resulting for the proposed structure is confirmed by the virtual absence of a dipole moment in *(3)* ($\mu = 0.18 \pm 0.15$ Debye; cyclohexane, 25 °C).

6) The experimentally detected diamagnetism corresponds to the noble gas configuration in *(3)*. Each one of the ethoxycarbonylcarbyne bridges acts as a three-electron ligand and thus resembles the monodentate (aryl)alkylcarbyne ligands[4].

Di-μ-ethoxycarbonylcarbynebis(tetracarbonylmanganese) (3):

All operations are performed in an inert atmosphere (N_2) using dry (Na/K) nitrogen-saturated solvents. Compounds *(1)* (1.28 g, 3 mmol)[5] and *(2)* (1.65 g, 6 mmol)[6] are refluxed in diethyl ether (200 ml) for 10 h. After removal of the solvent, the benzene-soluble portion of the crude product is filtered (G4 frit). The filtrate is concentrated by evaporation and then chromatographed on silica gel (Merck 7734, activity grade I; water-cooled column). Elution with *n*-hexane affords a little *(2)* as light yellow zone. With *n*-hexane/benzene (5:1) an orange-yellow zone migrates which affords fine needles of *(3)* on concentration and repeated crystallization (*n*-pentane, −85 °C); yield 570 mg (38 %).

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CAS Registry numbers: *(1)*, 20363-85-3; *(2)*, 14516-54-2; *(3)*, 53352-70-8

[1] Complex Chemistry of Reactive Organic Compounds.– Parts 1—3: a) *W. A. Herrmann*, Angew. Chem. *86*, 345 (1974); Angew. Chem. internat. Edit. *13*, 335 (1974); b) *ibid.* *86*, 556 (1974), and *13*, 599 (1974), respectively; c) Chem. Ber. *107*, 2899 (1974).

[2] *T. DoMinh, H. E. Gunning*, and *O. P. Strausz*, J. Amer. Chem. Soc. *89*, 6785 (1967); *O. P. Strausz, T. DoMinh*, and *J. Font*, *ibid.* *90*, 1930 (1968).

[3] *M. A. El-Sayed* and *H. D. Kaesz*, Inorg. Chem. *2*, 158 (1963); *L. E. Orgel*, *ibid.* *3*, 303 (1964).

[4] *E. O. Fischer, G. Kreis, C. G. Kreiter, J. Müller, G. Huttner*, and *H. Lorenz*, Angew. Chem. *85*, 618 (1973); Angew. Chem. internat. Edit. *12*, 564 (1973).

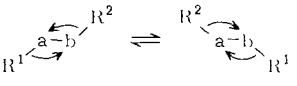
[5] *E. Buchner*, Ber. Deut. Chem. Ges. *28*, 215 (1895).

[6] *E. W. Abel* and *G. Wilkinson*, J. Chem. Soc. *A 1959*, 1501.

Dyotropic Rearrangement of (Silyl)methyl Silyl Ethers[1][**]

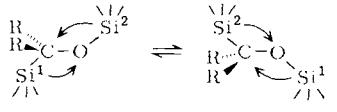
By *Manfred T. Reetz, Miroslav Kliment*, and *Michael Plachky*[*]

Dyotropic rearrangements of the type *(1)* ⇌ *(2)* are thermally forbidden pericyclic $[_\sigma 2_s + _\sigma 2_s]$ processes[2]. However, if the migrating groups possess low-lying unoccupied orbitals of proper symmetry then the constraints imposed by orbital symmetry can be lifted[3].



(1) *(2)*

In order to test this hypothesis we synthesized compounds of type *(3)*[4], expecting the silyl groups having empty d orbitals to undergo positional exchange on thermolysis.



(3) *(4)*

(a): R + R = biphenyl-2,2'-ylene
Si^1 = trimethylsilyl
Si^2 = [D_9]-trimethylsilyl

(b): R + R = biphenyl-2,2'-ylene
Si^1 = trimethylsilyl
Si^2 = dimethylphenylsilyl

If compounds *(3)* are heated to 140 to 175 °C in inert solvents (*e.g.* benzene) the rearrangement products are indeed formed, the reaction leading to an equilibrium: *(3a)*:*(4a)* = 1.0 (164 °C); *(3b)*:*(4b)* = 0.9 (164 °C). Thermolysis of compounds *(4)* prepared by an independent route[4] led to the same equilibrium. No by-products were formed.

Mechanistic evidence resulted from the following findings:

1) Crossover experiments showed the reaction to be strictly *intramolecular*.

2) The rate of rearrangement depends only slightly on the polarity of the solvent: k_{rel} for *(3b)* → *(4b)*: 1.0 (benzene): 1.8 (*o*-dichlorobenzene): 3.5 (propylene carbonate).

3) Activation parameters for *(3b)* → *(4b)*, measured in benzene, are: $E_a = 31.1 \pm 0.6$ kcal mol^{-1}; $\Delta H^{\neq} = 30.3 \pm 0.6$ kcal mol^{-1}; $\Delta S^{\neq} = -8.6 \pm 0.8$ cal mol^{-1} deg^{-1}.

4) Stereochemical investigations show that a chiral silyl group[5] migrates from the C to the O atom with >95 % *retention* of configuration. The same applies to the reverse reaction from the O to the C atom.

The results fail to support the occurrence of ions, zwitterions, or radicals. They are best compatible with a dyotropic mechanism in which both silyl groups undergo migration. Whether a symmetrical transition state is involved, or whether one of the silyl groups migrates faster than the other, cannot be deduced from the information available. However, the similarity between the present activation parameters and those for the related rearrangement of (silyl)methyl allyl ethers[1],

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in which a silyl and an allyl group migrate, can be regarded as evidence in favor of an asymmetrical transition state. In any case, the silyl group shift brings about a kind of Walden inversion of the substituents attached to the stationary C atom. This prediction is currently under investigation[6].

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German version: Angew. Chem. 86, 899 (1974)

[1] Dyotropic Rearrangements, Part 5.—Part 4: *M. T. Reetz*, Angew. Chem. 86, 416 (1974); Angew. Chem. internat. Edit. 13, 402 (1974).

[2] *M. T. Reetz*, Angew. Chem. 84, 161 (1972); Angew. Chem. internat. Edit. 11, 129 (1972).

[3] *M. T. Reetz*, Tetrahedron 29, 2189 (1973).

[4] Prepared by silylation of the corresponding (silyl)methyl alcohols. The structure was confirmed by spectroscopy and analysis.

[5] Methyl-1-naphthylphenylsilyl group. Cf. *L. H. Sommer, C. L. Frye, G. A. Parker*, and *K. W. Michael*, J. Amer. Chem. Soc. 86, 3271 (1964).

[6] This investigation should also yield information about possible alternative mechanisms (*e.g.* oxygen ylide formation).

Octopus Molecules[**]

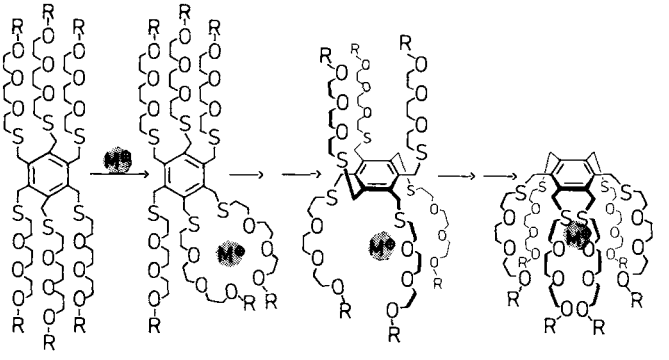
By *Fritz Vögtle* and *Edwin Weber*[*]

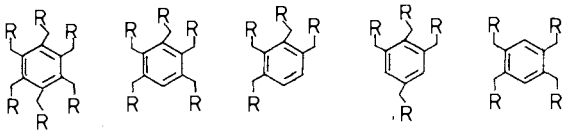
Knowledge gained about "coronates"[1], catapinates, and cryptates[2] has induced us to synthesize acyclic but "many-armed" polyether, complex-forming ligands of type *(1a)*, in which each "arm" is fitted with numerous donor atoms. Here we not only report about the unusual complexing tendency of such ligands but also show how their conformational mobility is impeded by spatial crowding.

The hexasubstituted benzene derivative *(1a)* containing 18 oxygen atoms is obtained as a yellowish, viscous oil ($\delta = 4.10$)[3], which is *insoluble in water*, on reaction of benzenehexakis(methanethiol) and 1-bromo-3,6,9-trioxatridecane ("1-bromotriethyleneglycol ω-butyl ether"). It is a remarkably powerful complex ligand for cations since a solution of *(1a)* in dichloromethane removes a great part of the picrate from 10^{-4} N aqueous alkaline-earth picrate solutions (Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}) and almost the entire salt from alkali-metal picrate solutions (Li^+, Na^+, K^+, Rb^+, Cs^+) from the aqueous into the organic phase[4].

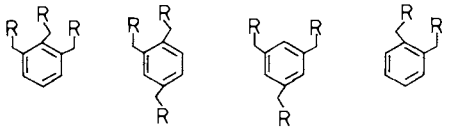
This occurs faster and more completely than can be achieved with known crown ethers[5]; only cryptate ligands such as "[2.2.2]" and "[2.2.1]" are equally effective. The usual oligoethers, glycols, and comparative substances such as 1-bromotriethyleneglycol ω-butyl ether and triethyleneglycol butyl ether have no such action under analogous conditions.

According to a study with space-filling models the unexpectedly strong complex formation by *(1a)* (which invites a study of polyfunctional acyclic biomolecules) must be accompanied by considerable conformational changes. It shows remarkable phenomenological parallelisms to the mode of food capture by an octopus using its suction pads[6].





(1) *(2)* *(3)* *(4)* *(5)*



(6) *(7)* *(8)* *(9)*

	R
(a)	S O O O C_4H_9
(b)	S O O CH_3
(c)	S-α-C_5H_5N
(d)	SCH_3
(e)	$SCH(CH_3)_2$
(f)	S-n-C_4H_9
(g)	S-n-$C_{12}H_{25}$
(h)	S-⬡
(i)	S-⬡
(k)	SO_2CH_3

Picric acid itself can also be easily extracted from aqueous solution by dichloromethane that contains an "octopus molecule" such as *(1a)*. Also remarkable is the, admittedly weak, complexing of cobalt thiocyanate by *(1a)* and its partial transfer into the dichloromethane phase. Heavy-metal salts such as $CuCl_2$, $NiCl_2$, $Ce(SO_4)_2$, $Pr(NO_3)_3$, and $Nd(NO_3)_3$ could not be extracted from water by dichloromethane solutions of *(1a)* or by crown ethers and "[2.2.2]" (under comparable conditions).

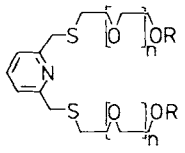
A distinct fall in complexing tendency occurs if the number of donor positions is decreased, either by shortening of the arms as in *(1b)* (colorless viscous oil; $\delta = 4.11$) or by successive diminution of their number. Among position isomers with equal numbers of arms the 1,3,5-isomer *(8)* and, on presence of only two substituents, the 1,2-disubstituted system *(9)* stand out for powerful ligand properties. *(8a)* is certainly less efficient than *(1a)* having three more arms, but it is more effective than *(6a)* and even than *(4a)*; here steric factors (see below), lipophilic character, and solubility properties of the ligand seem to be important[2].

Complex-formation by the crystalline potential ligand *(1c)* (m.p. 262 °C, dec.; $\delta = 4.54$, in pyridine) that contains six pyridine rings is hard to establish because of the sparing solubility. The *water-insoluble* pyridine derivatives *(10)* and *(11)* (colorless viscous liquids; $\delta = 3.97$ and 3.85, respectively) have special phase-transfer properties: although alkaline-earth- and alkali-metal picrates cannot be thereby extracted from aqueous solution, picric acid dissolved in water is rapidly and completely transferred into the organic phase (dichloromethane). This does not occur with comparable substances such as pyridine under analogous conditions. Further, in methanol *(10)* forms

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a deep-green copper(II) complex, but no interaction is observable with other heavy-metal ions such as Co^{2+} or Ni^{2+}.



(10), n=1, R = CH_3
(11), n=2, R = C_4H_9

Oxygen-free hexasubstituted benzene derivatives *(1d)*—*(1f)*, *(1h)*[7] as well as *(1g)*, *(1i)*, and the hexasulfone *(1k)* were investigated for comparison and naturally have no complex-ligand properties.

The free ligand molecule *(1a)* gives an unexpected ^{1}H-NMR spectrum (Fig. 1), from which conclusions can be drawn about intramolecular mobility phenomena that are slow on the NMR time scale: the signals of the α- and γ-methylene protons are considerably broadened at room temperature. Increase in temperature sharpens all the signals, cooling broadens them further. Clearly there is steric overcrowding in the hexasubstituted system *(1)*[8].

shorter chains, as is shown by the very marked broadening of the signals of the α-methylene protons.

Whereas *(1h)* shows a barely broadened benzyl singlet (δ = 4.29) in spite of the six space-filling phenyl substituents, the sulfone *(1k)* (m.p. >350 °C, dec; δ = 5.13) exhibits somewhat broadened CH_2 signals even at room temperature. Remarkable also is the finding that introduction of six sterically demanding 2,6-dimetbylphenyl groups as in *(1i)* (m.p. 248 to 251 °C; δ = 3.76)[3] does not notably increase the steric crowding over *(1h)*; the 36 CH_3 protons appear as a sharp singlet [δ(CH_3) = 2.30 in $CDCl_3$].

As the number of side chains decreases, the signal broadening becomes less; the steric interactions presently appear to be in the order *(1a)* > *(2a)* (δ = 3.59—4.18) > *(3a)* (δ = 4.02, 4.23) > *(4a)* (δ = 3.77, 3.92, 4.10) > *(5a)* (δ = 4.2); and with *(6a)* (δ = 4.17, 3.98), *(7a)* (δ = 3.98), *(8a)* (δ = 3.83), and *(9a)* (δ = 4.02) interaction is no longer unequivocally detectable. Replacing a benzene-hydrogen atom that is not contiguous to the interacting substituents, as in the change from *(6a)* to *(4a)* or from *(7a)* to *(5a)*, may increase the hindrance to rotation, and this can be interpreted as a steric buttressing effect[11].

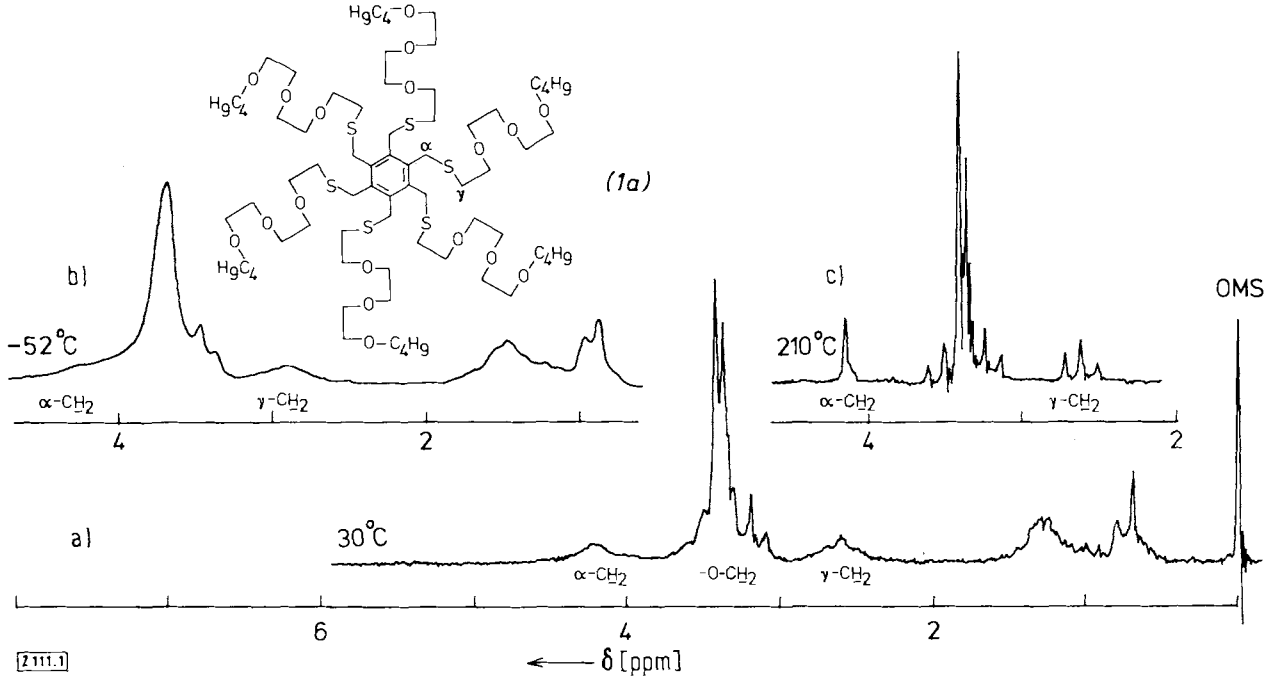


Fig. 1. ^{1}H-NMR spectrum of *(1a)* at several temperatures. a) and c) in diphenyl ether, b) in $CDCl_3$; 60 MHz. OMS = octamethylcyclotetrasiloxane.

We wished to discover whether this steric effect (a) was a characteristic of the polyoxa compounds *(1a)* and *(1b)* for which the heteroatoms or coiling of the arms would be responsible, or (b) was to be ascribed in general to steric overcrowding in the persubstituted benzene ring; so we studied the proton resonance of the hexaorganothio compounds *(1d)*—*(1i)* which contain substituent chains of different lengths and different branching, as well as the hexasulfone *(1k)*. It transpired that here too broadening of the benzylic CH_2 signals could occur: whereas no steric hindrance of rotation could be detected in *(1d)* (δ = 4.12) or in hexakis(bromomethyl)benzene[9] (δ = 4.71 in $CHBr_3$ at 158 °C)[10] by ^{1}H-NMR spectroscopy, we found somewhat broadened signals of the α- and γ-methylene-protons already for *n*-butyl substitution *(1f)* (δ = 4.14). The longer alkyl chains of, particularly, *(1g)* (m.p. 38—39 °C; δ = 4.16) with their greater effective steric requirements, cause steric overcrowding that is greater than for the

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[1] Proposal for designation of crown ether complexes. *P. Neumann* and *F. Vögtle*, unpublished.

[2] Reviews: *C. J. Pedersen* and *H. K. Frensdorff*, Angew. Chem. *84*, 16 (1972); Angew. Chem. internat. Edit. *11*, 16 (1972); *J. M. Lehn*, Struct. Bonding *16*, 1 (1973); *F. Vögtle* and *P. Neumann*, Chem.-Ztg. *97*, 600 (1973); *D. J. Cram* and *J. M. Cram*, Science *183*, 803 (1974); see also: *D. St. C. Black* and *A. J. Hartshorn*, Coord. Chem. Rev. *9*, 219 (1973).

[3] NMR signal (ppm) of the α-CH_2-protons (in $CDCl_3$ unless otherwise stated).

[4] For method see *C. J. Pedersen*, J. Amer. Chem. Soc. *92*, 391 (1970).

[5] This is true also for the *meta*-bridged crown ethers described by us [*F. Vögtle* and *E. Weber*, Angew. Chem. *86*, 126 (1974); Angew. Chem. internat. Edit. *13*, 149 (1974)].

[6] *H. Wurmbach*: Lehrbuch der Zoologie. Gustav Fischer Verlag, Stuttgart 1970.—Octopus molecules with eight and ten arms may be synthesized using naphthalene and biphenyl systems, respectively.

[7] *H. J. Backer*, Rec. Trav. Chim. Pays-Bas *54*, 745, 905 (1935).

[8] *K. Mislow*, Introduction to Stereochemistry. W. A. Benjamin, Inc., New York 1966; *H. A. Staab*: Einführung in die theoretische organische Chemie. Verlag Chemie, Weinheim, 4th Edit. 1966; *M. S. Newman*: Steric Effects in Organic Chemistry. Wiley, New York 1956. See also: *B. Nilsson, P. Martinson, K. Olsson*, and *R. E. Carter*, J. Amer. Chem. Soc. *96*, 3190 (1974).

[9] X-ray structure analysis: *P. Marsau*, Acta Crystallogr. *18*, 851 (1965).

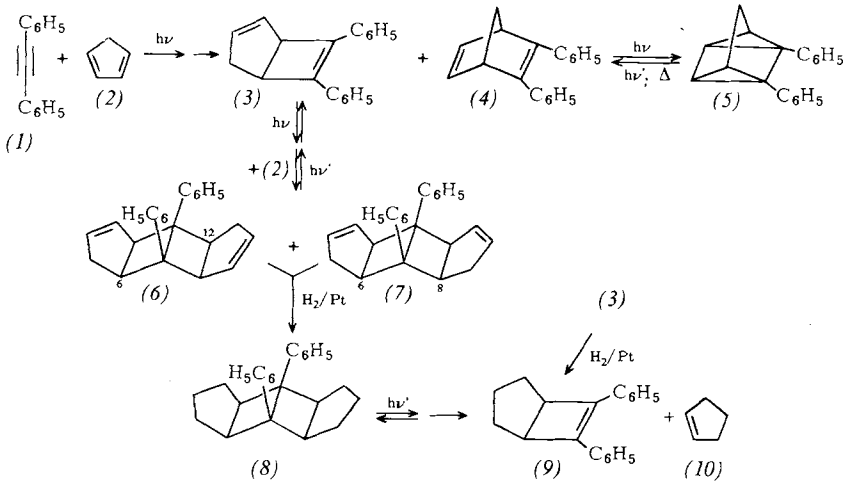
[10] *P. Neumann*, Dissertation, Universität Heidelberg 1973.

[11] *M. Rieger* and *F. H. Westheimer*, J. Amer. Chem. Soc. *72*, 19 (1950); *W. Theilacker* and *R. Hopp*, Chem. Ber. *92*, 2293 (1959); *W. Theilacker* and *H. Böhm*, Angew. Chem. *79*, 232 (1967); Angew. Chem. internat. Edit. *6*, 251 (1967). Review: *E. L. Eliel*, Stereochemistry of Carbon Compounds, McGraw-Hill, New York 1962.

1,4-Diphenylbicyclo[2.2.0]hexanes from 1,2-Diphenylcyclobutenes[**]

By *Gerd Kaupp, Christoph Küchel*, and *Inge Zimmermann*[*]

All previously reported [2π+2π] photocycloadditions of diphenylacetylene to isolated or conjugated double bonds have led only to 1,2-diphenylcyclobutene derivatives or to the valence isomers derivable from them[1]. We now report intermolecular consecutive additions and preparatively interesting quantum yields of the photosynthesis of 1,4-diphenylbicyclo[2.2.0]hexanes from 1,2-diphenylcyclobutenes. Because of the longer lifetime of the fluorescent excited states and, presumably, substantial chromophore leveling, the conditions for such additions are much more favorable than in the case of open-chain *cis*-stilbenes, which do not undergo photocycloadditions[2].



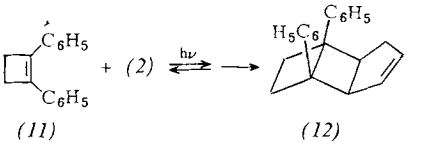
The photolysis of diphenyl acetylene *(1)* in cyclopentadiene *(2)* (pyrex filter, −30°C) leads—undoubtedly *via (3)* (m.p. 82—83°C)—to *(6)* (m.p. 132.5—134°C) and *(7)* (m.p. 110°C) in 32% and 11% yields, respectively[2]. Other products formed include *(5)*, which is formed in 10% yield *via* the photo-Diels-Alder adduct *(4)*[3], some polymers, and alteration products formed during the chromatographic separation.

On catalytic hydrogenation, *(6)* and *(7)* both afford *(8)* (m.p. 113—114°C). They can, however, be readily distinguished by their ^{1}H-NMR spectra: All conceivable isomers of structure *(6)* possess a twofold axis of symmetry, and the resonances H^6/H^{12} give rise to a 7-line spectrum, degenerate in the center (100 MHz; τ = 6.75 ppm; $\Delta\nu_{1/2}$ = 1.8; J = 9.0, 6.5, 2.5 Hz). In contrast, H^6 and H^8 in *(7)* are subject to different anisotropic effects owing to the asymmetrically arranged phenyl groups, and their resonances at τ = 6.45—6.85 ppm give rise to three broad absorptions ($\Delta\nu_{1/2}$ = 3.0, 4.5, and 3.0 Hz). In all cases the sterically more favorable *exo*-arrangement of the two five-membered rings is confirmed by the symmetry properties of the non-superposed ^{1}H-NMR multiplets.

Characteristically structured UV-spectra (O/O transitions at 271 nm; ε = 370, 400, 435) and fluorescence spectra (ϕ_{fl} = 0.0049, 0.0086, 0.0049) serve for the detection of non-conjugated phenyl groups in *(6)*, *(7)*, and *(8)*, respectively.

The primary product *(3)* [λ_{max} = 280 (sh, 8800); 304 (15000); 311 (15000); 327 (sh, 9300)] is obtained uniformly by irradiation (253.7 nm) of *(6)* and *(7)* at −190°C[2]. Correspondingly, irradiation of *(8)* affords *(9)*. *(6)*, *(7)*, and *(8)* photolyze without phosphorescence in the rate ratio 5.4 : 1 : 1.1. In agreement with the two-step mechanism for the photocleavage of four-membered rings[3,4], there is no quantitative correlation between fluorescence intensity (see above) and photoreactivity. Thus it should not be expected that different benzylic C—C bonds will be cleaved with the same probability, nor that the resulting different diradicals[3,4] will be stabilized to reactant and product in the same proportion.

The isolation of *(3)* and *(9)* permits a check on the mechanistic considerations. Both fluoresce intensely (ϕ_{fl} = 0.66 and 0.69, respectively; cyclohexane) and photoadd to undiluted cyclopentadiene *(2)* (λ > 315 nm; −10°C) to give *(6)* and *(7)* (in the ratio 3 : 1)[5], and probably *exo,exo*-1.7-diphenyltetracyclo[5.5.0.0^{2,6}.0^{8,12}]dodeca-3-ene [*i.e.*, *(6)* or *(7)* with one hydrogenated double bond]. A preparative application consists in the corresponding reaction of *(11)*[6] to give *(12)* (m.p. 77°C; yield: 59%)[2]. The fluorescence intensities of *(3)*, *(9)*, and *(11)* (also no phosphorescence at −196°C) in cyclopentadiene are reduced to 1/6, 1/5, 1/10, respectively, compared to those in cyclohexane.



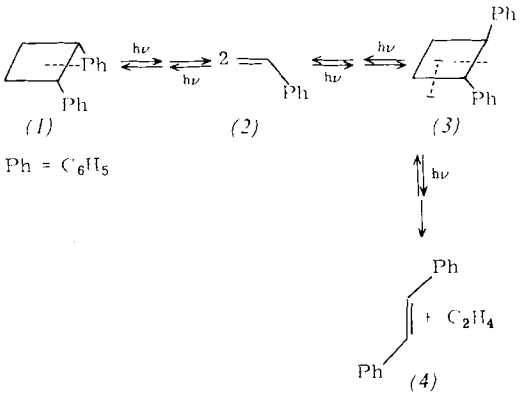
The considerable UV quantum yields[3] for the consumption of the *cis*-stilbene components *(3)*, *(9)*, and *(11)* (φ = 0.50, 0.44, and 0.57, respectively; 0—90% reaction) underline the

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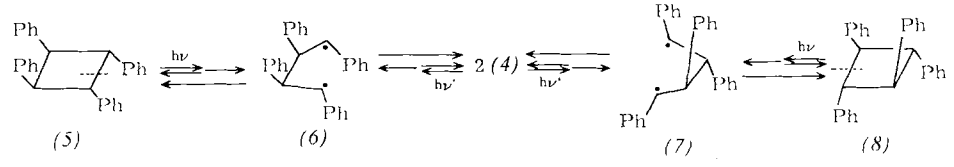
[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

potential usefulness of such singlet reactions in the synthesis of other 1,4-diphenylbicyclo[2.2.0]hexanes[7], even though *(1)*, together with other byproducts that are more difficult to characterise and are easily decomposed, and some polymers are also formed in preparative experiments.

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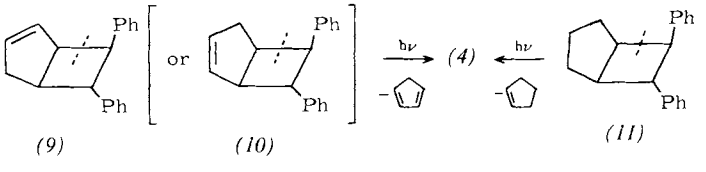


This "*cis*-effect" can be demonstrated quite clearly, for example, with the stilbene photodimers *(5)* and *(8)*, which are obtainable with self-quenching in yields of 47% and 23%, respectively[1a]. *(5)* ($\phi_{fl} = 0.0072$; $\lambda_{fl}^{corr} = 275$ sh, 282, 287, 295 sh nm; cyclohexane; 20°C) decomposes 3 times faster than *(8)*

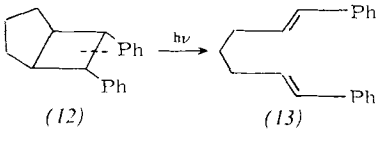


($\phi_{fl} = 0.024$) into two molecules of *(4)* (no side-reactions at −190°C; no phosphorescence); once again there is a higher probability for cleavage of a *cis* disubstituted bond.

Since no principle of microscopic reversibility of forward and reverse reactions is involved, it is not yet possible to calculate the stabilization ratios of *(6)* and *(7)* (cleavage and ring formation) which determine the quantum yields. The product-determining action of the *cis*-effect in the primary cleavages (diradical formation) is however sufficient for an understanding of the orientation selectivities. Thus *(9)* [or *(10)*?] like *(11)*[1a,7] photolyzes (253.7 nm; −190°C) with release of stilbene *(4)*, even though the less delocalized diradicals are formed in these processes [cf. *(3)*].



In contrast, under the same conditions *(12)* expectedly undergoes a valence isomerization to give *(13)* [cf. *(1)* and *(5)*].



Condensed four-membered rings with planar cyclic chromophores necessarily decompose into two components as in *(14)*[3], *(15)*[3], and *(16)*[9], since rupture of the central σ bonds would not lead to steric relief. As is to be expected,

[1] *S. P. Pappas* and *B. C. Pappas*, Tetrahedron Lett. *1967*, 1597; *O. L. Chapman* and *W. R. Adams*, J. Amer. Chem. Soc. *90*, 2333 (1968); *M. P. Servé* and *H. M. Rosenberg*, J. Org. Chem. *35*, 1237 (1970); *33*, 1653 (1968); *A. I. Meyers* and *P. Singh*, *ibid.* *35*, 3022 (1970); *G. Sugowdz*, *P. J. Collin*, and *W. H. Sasse*, Austral. J. Chem. *26*, 147 (1973); references to be found there to previous work too.

[2] *G. Kaupp* in Houben-Weyl: Methoden der Organischen Chemie. Thieme, Stuttgart. Vol. IV/5, in press. All the new compounds gave correct C H analyses; UV-, and fluorescence spectra as well as ^{1}H-NMR spectra are in agreement with the given structures.

[3] *G. Kaupp*, Liebigs Ann. Chem. *1973*, 844.

[4] *G. Kaupp*, Angew. Chem. *86*, 741 (1974); Angew. Chem. internat. Edit. *13*, 817 (1974); Angew. Chem., in press.

[5] An unequivocal prediction of this ratio is so far impossible owing to the lack of microscopic reversibility.

[6] *R. M. Dodson* and *A. G. Zielske*, J. Org. Chem. *32*, 28 (1967).

[7] A 1:2 addition product has been obtained in 7% yield from *(1)* and norbornadiene: *T. Kubota*, *K. Shima*, and *H. Sakurai*, Chem. Commun. *1971*, 360.

Orientation in Photochemical Cyclobutane Cleavages: *cis*-Effect[**]

By *Gerd Kaupp*[*]

The well-known [2σ→2π] photocleavage of cyclobutane derivatives[1] reveals some interesting orientation selectivities, in spite of the generally large excess of energy in the electronically excited state. We now report on the results of photolysis of phenyl-substituted cyclobutanes which explain these orientations on the basis of empirical-experimental mechanisms with intermediate products without calculation and without postulation of energetically most favorable reactionpaths[1b,2,3,4].

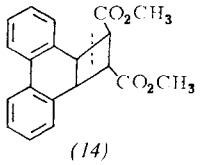
Irradiation of *(1)* or *(3)* (λ = 253.7 or 250 nm) affords *(2)* together with polymers and products that absorb at long wavelengths[5]. Only irradiation of *(3)* leads also to formation of *(4)* *via* the less stabilized diradical[2] (1% at −190°C and 10% conversion). *(3)* fluoresces three times more intensely[6] and photolyzes at −190°C five times more slowly than *(1)* (with uniform cyclobutane cleavages).

Cleavage of the *cis*-disubstituted bond in *(1)* is particularly favored, for this leads to relief of a large part of the steric strain.

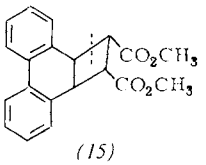
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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

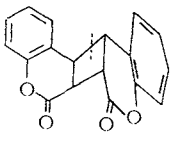
(14) photolyzes faster than *(15)* (*cis*-effect) and with partial formation of *(15)*[2,3]. Similarly clear are the differences in mode of cleavage in the case of *(16)*[9] and its product of hydrolysis *(17)*[10].



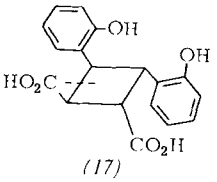
(14)



(15)

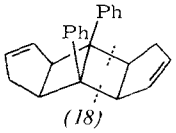


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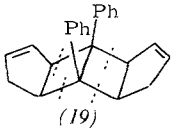


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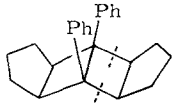
In the photolysis of cyclobutanes with four substituents in *cis*-positions no high selectivity of orientation can be expected. *(18)*, *(19)*, and *(20)*, which photochemically (at −190 °C) uniformly lose one of the five-membered rings[8], are conformationally fixed special cases.



(18)



(19)



(20)

In contrast to the primary cleavages indicated in the formula diagram, steric hindrance between phenyl and methylene groups would, according to molecular models, increase in the first place through stretching of the central four-membered ring-bonds.

It is not certain whether such processes nevertheless occur, being quantum-consuming but chemically unsuccessful[11].

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[1] Recent reviews: a) *G. Kaupp*, in Houben-Weyl: Methoden der Organischen Chemie, Thieme, Stuttgart, Vol. IV/5, in press; b) *G. Kaupp*, Liebigs Ann. Chem. *1973*, 844.

[2] *G. Kaupp*, Angew. Chem., in press.

[3] *G. Kaupp*, Angew. Chem. *85*, 766 (1973); Angew. Chem. internat. Edit. *12*, 765 (1973).

[4] Presented at the V. International IUPAC Symposium on Photochemistry (July 1974) in Enschede, Netherlands [Manuscripts of Contributed Papers: No. 30, p. 99 (1974)].

[5] Rearrangement products have been isolated from *(3)*: *M. Sauerbier*, Chem.-Ztg. *96*, 530 (1972).

[6] $\lambda_{fl}^{corr} = 283$ nm; after a short while fluorescence of *(2)* superimposes: $\lambda > 293$ nm. Here, as in the case of the other compounds, the corrected fluorescence excitation spectra (240 nm up to the longwave absorption boundary) are in complete agreement in all respects with the UV spectra.

[7] All the new compounds have been characterized by elementary analysis and by spectroscopy (cf. Ref. [8]).

[8] *G. Kaupp, C. Küchel*, and *I. Zimmermann*, Angew. Chem. *86*, 740 (1974); Angew. Chem. internat. Edit. *13*, 740 (1974).

[9] *C. H. Krauch, S. Farid*, and *G. O. Schenck*, Chem. Ber. *99*, 625 (1966).

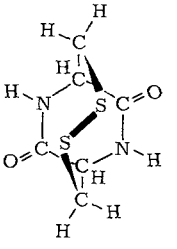
[10] *M. Hasegawa* and *Y. Suzuki*, Chem. Lett. *1972*, 317.

[11] Cf. *G. Kaupp*, Angew. Chem. *83*, 361 (1971); Angew. Chem. internat. Edit. *10*, 340 (1971).

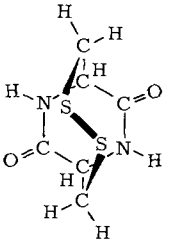
Temperature-Induced Change in Helicity of the Inherently Dissymmetrical Disulfide Group in Cyclocystine[**]

By *Günther Jung* and *Michael Ottnad*[*]

Particular importance attaches to cyclo-L-cystine (3,4-dithia-7,9-diazabicyclo[4.2.2]decane-8,10-dione) *(1)* as a test case for demonstrating the validity of theoretical concepts on the chiroptical properties of the disulfides. *(1)* contains a boat-shaped dioxopiperazine ring which is bridged by a disulfide group having an angle of twist of $\phi = 90°$[1]. Theoretically, a molecule containing a disulfide group twisted at such an angle should not exhibit any optical activity in the region of the longwave disulfide absorption at 245 nm[2]. This prediction has been substantiated (Fig. 1). The negative Cotton effect corresponds to the n-π* transition of *cis*-amides. The octet rule for carbonyl compounds can explain the presence of a *P*-helical disulfide bridge [as in *(1a)*][1]. The Cotton effect at 194 nm corresponds to a superposition of the π-π* transition of the amide groups and a disulfide transition.



P (1a)



M (1b)

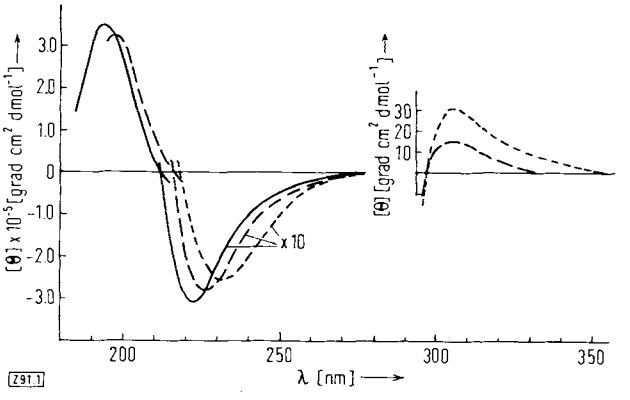


Fig. 1. CD spectra of *(1)* in trifluoroethanol (——), methanol (– –), and dioxane (– – – –).

The high rotatory power can be due to the conformational rigidity of *(1)* and to the favorable geometrical arrangement of the *cis*-amide groups for electrical dipole-dipole interactions. We have found, as expected, that *(1)* has a less temperature-dependent CD (Fig. 2) than other cystine compounds[3]; the change of CD with temperature is characteristic for diastereoisomers which interconvert. Below 40 °C the more stable *P*-helical diastereoisomer *(1a)* predominates, while above 40 °C the population of the *M*-helical form *(1b)*, with its less negative Cotton effect, increases. The temperature dependence in ethanol and in 0.1 N HCl differs considerably from that in trifluoroethanol. The stronger hydrogen-bonding tri-

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fluoroethanol stabilizes mainly the conformation *(1a)*. As expected, the Cotton effect of the n-π^* amide transition is shifted hypsochromically with increasing polarity of the solvent.

In contrast, the Cotton effect at 305 nm is less temperature dependent and not to be ascribed to the disulfide group; a dependence of its position and/or ellipticity on the solvent can hardly be established. This previously unobserved Cotton effect can certainly not arise from an impurity, for highly pure crystals were employed in the investigations. It is conceivable that a positive Cotton effect above 300 nm (possibly a CT transition analogous to that in epidithiopiperazinediones[4]) is superimposed by the negative amide Cotton effect such that it gives an apparent positive maximum above 300 nm.

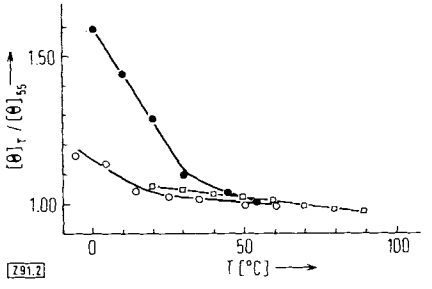


Fig. 2. Temperature dependence of the Cotton effect at about 225 nm in trifluoroethanol (● --●), ethanol (96 %) (○—○), and 0.1 N HCl (□ --□).

The ^{13}C-NMR spectrum of *(1)* in D_6-DMSO at temperatures below 45 °C shows three weak signals besides the three intense peaks (Fig. 3). The stronger signal of the carbonyl carbon lies at low field, which, independently of the CD, indicates the *P*-conformation for the disulfide bridge in which the sulfur atoms and the carbonyl group are closely proximate[5], the carbonyl carbon atom being more strongly deshielded than that in the *M*-helical molecule, whose ^{13}C signal was previously not observed[11].

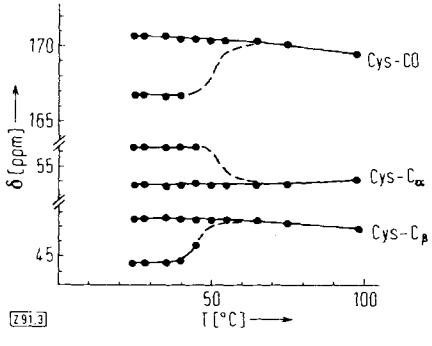
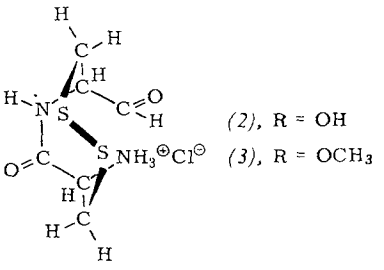


Fig. 3. Temperature dependence of the ^{13}C-NMR signals of *(1)* in D_6-DMSO.

Despite the weakness of the coalescence-point method in the determination of energy barriers from ^{13}C-NMR spectra[6], the lower limit of $\Delta G^{\neq}$ for rearrangement of the *P*-helical conformation of the disulfide bridge into the *M*-helical form can be estimated. Values of 15.6—16.0 kcal/mol are obtained. The highest previously observed rotation barriers about the disulfide group, which were measured on sterically very hindered diaryl disulfides, amounted to 15.7 kcal/mol[7] and likewise can only be considered as a lower limit value for this process. The intensities of the ^{13}C-NMR signals of *(1a)* and *(1b)* give the proportion of the less stable *M*-helical conformers *(1b)* at 25 °C as 15—20 %. Since the relaxation times of the aliphatic C atoms of *(1a)* and *(1b)* are comparable, this estimation is acceptable.



(2), R = OH
(3), R = OCH_3

Conformational calculations on L-cysteinylcysteine disulfide indicate a slightly nonplanar *cis*-amide group and give similar bond lengths and angles as in open chain cystine peptides. The total energies of the *P*- and *M*-conformations should differ only slightly (0.6 kcal/mol)[8]. In contrast to the CD spectrum of *(1)*, the spectra of L-cysteinylcysteine disulfide hydrochloride *(2)* and its methyl ester *(3)* show strongly reduced ellipticities and a reversal of sign, thus indicating lack of interaction between the amide groups and an increased flexibility of the disulfide group[9]. Hence, together with *(1)*, compounds *(2)* and *(3)* are the only examples known so far of compounds with inherent dissymmetrical disulfide groups without optical activity in the region of the longwave disulfide absorption.

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[1] *B. Donzel, B. Kamber, K. Wüthrich*, and *R. Schwyzer*, Helv. Chim. Acta 55, 947 (1972).

[2] *R. W. Woody*, Tetrahedron 29, 1273 (1973).

[3] a) *L. Flohé, H. Ch. Benöhr, H. Sies, H. D. Waller*, and *A. Wendel*: Glutathione. Thieme, Stuttgart 1974; b) *M. Ottnad, C. Ottnad, P. Hartter*, and *G. Jung* in [3a], p. 20ff.; c) *G. Jung, M. Ottnad*, and *M. Rimpler*, Eur. J. Biochem. 35, 436 (1973); d) *M. Ottnad, C. Ottnad, P. Hartter*, and *G. Jung*, Tetrahedron, in press; e) *T. Takagi* and *N. Ito*, Biochim. Biophys. Acta 257, 1 (1972); f) *T. Takagi, R. Okano*, and *N. Ito, ibid. 310*, 11 (1973).

[4] *R. Nagarajan* and *R. W. Woody*, J. Amer. Chem. Soc. 95, 7212 (1973).

[5] *G. Jung, E. Breitmaier*, and *W. Voelter*, Eur. J. Biochem. 24, 438 (1972); *G. Jung, E. Breitmaier, W. A. Günzler, M. Ottnad, W. Voelter*, and *L. Flohé* in [3a], p. 1ff.

[6] *S. Berger*, Dissertation, Universität Tübingen 1973, p. 58ff.; *D. K. Dalling, D. M. Grant*, and *L. F. Johnson*, J. Amer. Chem. Soc. 93, 3678 (1971); *O. A. Gansow, J. Killough*, and *A. R. Burke, ibid. 93*, 4297 (1971).

[7] *H. Kessler* and *W. Rundel*, Chem. Ber. 101, 3350 (1968).

[8] *R. Chandrasekaran* and *R. Balasubramanian*, Biochim. Biophys. Acta 188, 1 (1969).

[9] *G. Jung* and *M. Ottnad*, unpublished.

Intracrystalline Reactivity of Phyllodisilicic Acid $(H_2Si_2O_5)_x$

By *Gerhard Lagaly, K. Beneke, P. Dietz*, and *Armin Weiss*[*]

It is generally difficult to characterize solid silicic acids. The ≥Si—OH groups are often of low thermal stability, so that even slight heating causes the structure to change by condensation to siloxane groups ≥Si—O—Si≤. Their acidity is low; in attempts to determine the amount of ≥Si—OH groups in aqueous media cleavage of siloxane groups cannot always be excluded with certainty and many reagents do not yield the correct value if the density of silanol groups is high.

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An exception is provided by the crystalline phyllosilicic acids which form characteristic intercalation complexes. This property is shown most markedly by the natural and synthetic silicic acid "H-magadiite" ($H_2Si_{14}O_{29}\cdot 5.4\,H_2O$)[1].

We report below about "phyllodisilicic acid" $(H_2Si_2O_5)_x$. According to X-ray diagrams three forms can be distinguished[2–5], but we investigated mainly form II. This is obtained by reaction of 80% sulfuric acid at 0°C with powdered α-$Na_2Si_2O_5$[2].

After refinement the relatively sharp powder diagram of form II has the axes (cf.[13]) $a_0 = 5.6_4$, $b_0 = 14.6_3$, and $c_0 = 29.7_1$ Å. According to the structure determination by *Liebau*, the SiO_4 tetrahedra are linked to form layers in such a way that twelve-membered siloxane rings are obtained. But unlike the "tetrahedral layers" in clay minerals, the free corners of the tetrahedrons (≥Si—OH groups) project alternately above and below the layer. In the free acid the layers are folded; the basal spacing $d_L = b/2$ is 7.3 Å.

The phyllodisilicic acids are considerably less reactive than H-magadiite. They do not form intercalation complexes by direct reaction with formamide, acetamide, urea, pyridine, pyridine *N*-oxide, or their methyl or ethyl derivatives. It is impossible to distinguish whether simple intercalation complexes have been formed or whether new silicates have arisen by acid-base reactions with retention of the layer structure. Reaction with aqueous hydrazine solutions increases the basal spacing d_L, from 7.3 Å to 9.8—10.5 Å, depending on the water content (Table 1). The increase in the basal spacing is of the same order of magnitude as in kaolinite (from 7.1_5 to 10.4 Å[6]). By washing with water the phyllodisilicic acid is reformed. Methylhydrazine ($pK_B = 7.9$) increases the basal spacing to 10.0 Å, but with *N*,*N'*-dimethylhydrazine ($pK_B = 7.5$) there is no reaction. This makes it clear that base strength is not alone decisive, and that steric effects play an appreciable role.

Table 1. Basal spacings d_L and methods of preparation of intercalation compounds of phyllodisilicic acid $(H_2Si_2O_5)_x$.

Intercalated compound	d_L [Å]	Preparation	pK_B [a]
		Direct reaction with	
N_2H_4	10.5	$N_2H_4\cdot 1H_2O$	
	10.1_5	$N_2H_4\cdot 2H_2O$	
	10.0	$N_2H_4\cdot 4H_2O$	
	9.9	$N_2H_4\cdot 6H_2O$	
	9.8	$N_2H_4\cdot 10H_2O$	
	9.8	$N_2H_4\cdot 50H_2O$	5.8
$N_2H_3CH_3$	10.0	Methylhydrazine	7.9
NH_3	9.8	Ammonia (1 N [a])	4.8
CH_3NH_2	10.0	Methylamine (40% [a])	3.3
$C_2H_5NH_2$	10.9	Ethylamine (33% [a])	3.2
Piperazine	11.0	Piperazine (sat. [a])	4.2
		By displacement of	
Piperidine	11.6	Ethylamine	2.9
Pyridine	13.4	Butylamine or hexylamine	8.7
Cyclohexylamine	18.3	Ethyl-, butyl-, or hexyl-amine	3.7
Aniline	22.0	Butylamine	9.4

[a] Aqueous solution

Aqueous NH_3, methylamine, and ethylamine react with expansion of the basal spacing to 9.8, 10.0, and 10.9 Å, respectively. Amines with longer chains do not react directly. If an excess of propylamine is allowed to react with the ethylamine compound, the ethylamine is displaced from the interlayer spaces and the propylamine compound is formed, the basal spacing increasing from 10.9 to 17.1 Å. The butylamine compound can be obtained analogously from the propylamine compound, and therefrom the pentylamine compound, *etc.* ("propping open"[7]). The displacement reactions are reversible.

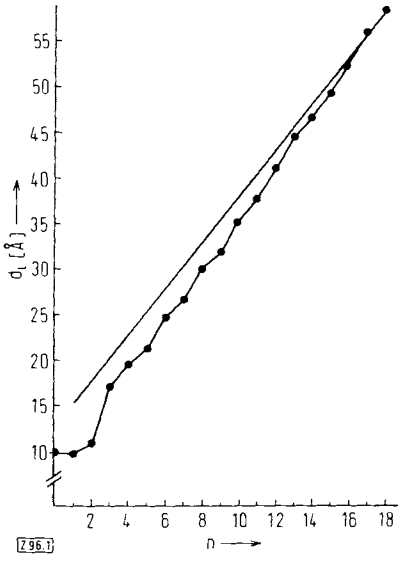
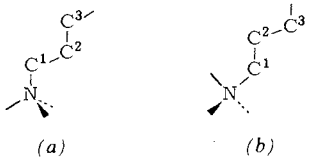


Fig. 1. Basal spacings d_L of intercalation compounds of phyllodisilicic acid with primary *n*-alkylamines as dependent on the number *n* of C atoms in the alkyl chain; -●- experimental values; ——— calculated for bimolecular layers of alkyl chains arranged perpendicularly to the layers according to the relation $d_L = 9.8 + 2 \times 1.26 \times n + 3$ [Å] (9.8 = basal spacing of the NH_3 compound; 1.26 = projection of the C—C bond on the chain long axis; 3 = van der Waals radius of the methyl terminal group).

Figure 1 shows the basal spacings of the *n*-alkylamine compounds with $n = 1$ to 18 C atoms in the alkyl chain. For $n > 2$ they increase linearly with chain length. The average increase is 2.8 Å/CH_2; this value is distinctly greater than the maximal value 2.5 Å that would be expected for a bimolecular arrangement of the alkylamine molecules in the interlayer spaces with their long axes standing perpendicular to the silicate layers. It must be assumed that the chains are tilted at an angle to the silicate layers and that the tilting angle increases with chain length up to 90°. This is shown also in the absolute values: Starting from the NH_3 compound ($d_L = 9.8$ Å) one calculates for perpendicularly arranged chains values of 33.0 and 58.2 Å for, respectively, 8 and 18 C atoms in the alkyl chain; observed values are 30.0 and 58.4 Å. Fitting the NH_2 groups to the puckered silicate layer probably forces an inclined orientation on the shorter alkyl chains. Increasing van der Waals energy with increasing chain length cause the tilting angle to approach 90°. A similar change in orientation was found in the complexes of transition-metal disulfides with alkylamines[8]. The inclination of the shorter alkyl chains is indicated also by the alternation of the basal spacings: the increase $\Delta d_L = d_L(n+1) - d_L(n)$ is larger for odd than for even *n*; and this hints to a specific orientation *(b)* of the NH_2 groups with respect to the silicate layer[9].



(a) *(b)*

Shortening of the shorter alkyl chains by formation of *gauche* bonds is presumably excluded, since this effect is normally favored with long alkyl chains[10].

The ethylamine or butylamine compound can be converted into other amine complexes (Table 1) too.

The amine can be washed out of *n*-alkylamine compounds by anhydrous ethanol, which is an indication in favor of existence of true intercalation compounds and against formation of *n*-alkylammonium silicates by direct acid-base reaction. The free d-orbitals of the Si atoms probably function as acceptors for the intercalated Lewis bases. It is possible that intercalation compounds of crystalline silicic acids may come to be used as models of adsorption systems with amorphous SiO_2 preparations.

The majority of the intercalation compounds are well ordered and the original silicic acid can be reformed in more or less well ordered state by cautious evaporation of the intercalated component or by its extraction with an inert solvent.

In some cases, *e. g.* with dimethyl sulfoxide, formation of intercalation compounds of phyllodisilicic acid is accompanied by large broadening of the (0*k*0) interferences, sometimes even by production of amorphous materials. Presumably the strong interactions between the intercalated molecules and the silicic acid layers change the folding and destroy the parallel orientation over large areas; if the intercalated molecules are removed the original order cannot be restored and hitherto unknown paracrystalline silicic acids result.

The intracrystalline reactivity of phyllodisilicic acid and the structural stability during the intercalation processes proved to be strongly dependent on the mode of preparation of the disilicic acid. Disilicic acid can be prepared not only by reaction of α-$Na_2Si_2O_5$ with 80% H_2SO_4 at 0°C[12], but also with 40% H_2SO_4, 1 N HCl, or H^+-ion exchangers at room temperature. The preparations at room temperature give nearly identical X-ray diagrams with only minor differences in the sharpness of the reflections in comparison with preparations at 0°C, but amorphous products with hydrazine hydrate. Probably at room temperature the folding of the layers becomes less regular and the regions of equal folding direction less extended. Aging phenomena[3, 4] connected with condensation of silanol groups play an important role.

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[1] *G. Lagaly, K. Beneke,* and *A. Weiss,* Z. Naturforsch. *28b*, 234 (1973).
[2] *R. Schwarz* and *E. Menner,* Ber. Deut. Chem. Ges. *57*, 1477 (1924).
[3] *E. Liebau,* Z. Kristallogr. *120*, 427 (1964).
[4] *F. Wodtcke* and *F. Liebau,* Z. Anorg. Allg. Chem. *335*, 178 (1965).
[5] *M.-Th. Le Bihan, A. Kalt,* and *R. Wey,* Bull. Soc. Fr. Mineral. Cristallogr. *94*, 15 (1971).
[6] *A. Weiss, W. Thielepape, W. Ritter, H. Schäfer,* and *G. Göring,* Z. Anorg. Allg. Chem. *320*, 183 (1963).
[7] *G. W. Brindley* and *S. Ray,* Amer. Mineral. *49*, 106 (1964).
[8] *A. Weiss* and *R. Ruthardt,* Z. Naturforsch. *28b*, 249 (1973).
[9] *G. Lagaly* and *A. Weiss,* Kolloid Z. Z. Polym. *238*, 485 (1970).
[10] *G. Lagaly* and *A. Weiss,* Angew. Chem. *83*, 580 (1971); *85*, 915 (1973); Angew. Chem. internat. Edit. *10*, 558 (1971); *12*, 850 (1973).

Crystal Structure of $(HgI)_2TiF_6$[**]

By *Klaus Köhler, Dietrich Breitinger,* and *Gerhard Thiele*[*]

Mercurioiodonium complexes of the composition $(HgI)_n^{n+}X^{n-}$ are formed as reaction products in the systems $Hg^{2+}/I^-/X^{n-}$ ($X^{n-} = TiF_6^{2-}$, ZrF_6^{2-}, SnF_6^{2-}, NO_3^-, and BF_4^-)[1]. Vibrational spectrometric investigations of the crystalline solids suggest a structure for the $(HgI)^+$ cation[2] consisting of planar chains with angular bonding at the iodine atom, as has been found for the isoelectronic AuI[3, 4].

The determination of the crystal structure of $(HgI)_2TiF_6$—$(HgI)_2ZrF_6$ and $(HgI)_2SnF_6$ are isotypic—was based on 490 independent reflections (255 with $I<3\sigma$) measured with a four circle diffractometer ($Mo_{K\alpha}$ radiation, graphite monochromator) in the range $0° < \vartheta \leq 22°$[5]. Refinement of the structural model obtained by Fourier methods led, after absorption correction[6], and with anisotropic temperature factors, to a final *R* factor of 0.083 (coordinates in Table 1).

Table 1. Atomic coordinates of $(HgI)_2TiF_6$.

Atom	Equiv. posn.	x	y	z
Hg	8g	0.2581	0.3583	0.25
I^1	4c	0.5	0.2329	0.25
I^2	4c	0.5	0.9742	0.25
Ti	4c	0	0.1092	0.25
F^1	4c	0	0.2371	0.25
F^2	4c	0	0.9821	0.25
F^3	16h	0.1769	0.1099	0.4205

Crystallographic data: Space group Cmcm-D_{2h}^{17}; $a=762.2\pm0.6$, $b=1492.0\pm0.9$, $c=761.3\pm0.9$ pm; $Z=4$; $d_{calc}=6.27$, $d_{exp}=6.15\,g\,cm^{-3}$.

Zigzag chains $^1_\infty[IHg_{2/2}]^+$ pass through the lattice parallel to the *a* axis (line group No. 10 of the Bhagavantam classification[7], factor group isomorphic to C_{2v}-mm); coplanar pairs of chains lie in planes with $z=0.25$ and $z=0.75$ (Fig. 1). Interatomic distances and bond angles are listed in Table 2.

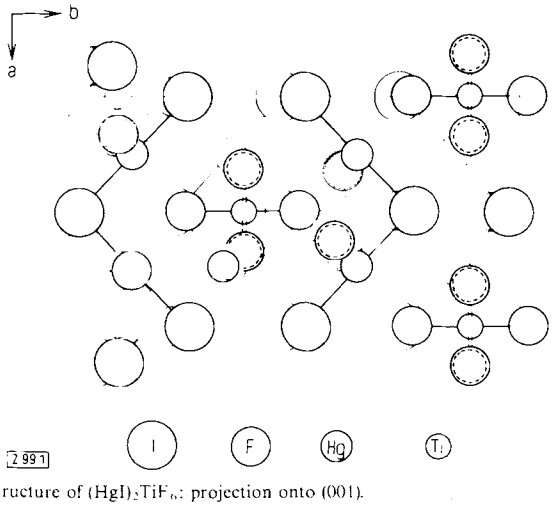


Fig. 1. Structure of $(HgI)_2TiF_6$: projection onto (001).

Table 2. Interatomic distances [pm] and bond angles (standard deviation in units of last decimal place given in parenthesis).

Hg–I^1	262.7(4)	Ti–F^1	190.8(60)
Hg–I^2	261.8(4)	Ti–F^2	189.6(60)
Hg–F^1	267 (4)	Ti–F^3	187.2(20)
Hg–F^2	264 (4)		
Hg–F^3	2×262 (4)		
Hg–I^1–Hg	89.4(2)° ≙ 1.560(3)rad		
Hg–I^2–Hg	97.2(2)° ≙ 1.696(3)rad		
I^1–Hg–I^2	175.8° ≙ 3.068 rad		

The chains are linked together in various ways *via* slightly deformed TiF_6^{2-} octahedra, such that the mercury atoms

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have a distorted octahedral environment. As a result of these interactions the bond angle at mercury deviates from the ideal value of 180° for sp or ds hybridization.

The bond angles at iodine determined from the vibrational spectra are in satisfactory agreement with the values determined by X-ray crystallography[8].

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CAS Registry Number: $(HgI)_2TiF_6$, 38702-77-1

[1] *K. Köhler*, Dissertation, Universität Erlangen 1973.

[2] *D. Breitinger* and *K. Köhler*, Inorg. Nucl. Chem. Lett. *8*, 957 (1972).

[3] *A. Weiss* and *A. Weiss*, Z. Naturforsch. *11b*, 604 (1956).

[4] *H. Jagodzinski*, Z. Kristallogr. Kristallgeometrie Kristallphys. Kristallchem. *112*, 80 (1959).

[5] We are grateful to Dr. *G. Liehr* for performing the measurements.

[6] *Th. Hahn*, Neues Jahrb. Mineral. Monatsh. *1960*, 25.

[7] *S. Bhagavantam* and *T. Venkatarayudu*: Theory of Groups and its Application to Physical Problems. Academic Press, New York 1969, Chap. II.

[8] *D. Breitinger* and *K. Köhler*, to be published.

Structure of Diimine: X-ray Diffraction Analysis of $N_2H_2[Cr(CO)_5]_2 \cdot 2THF$[**]

By *Gottfried Huttner*, *Wolfgang Gartzke*, and *Kurt Allinger*[*]

Investigations on the structure and properties of diimine, HN=NH, the simplest azo compound, have so far not been fully satisfactory owing to the instability of the compound. *Wiberg et al.*[1] have recently found a preparative method which provides access to practicable amounts of free diimine, but its ready decomposition (which in the solid state begins at −180 °C), considerably hampers detailed structural investigations[2].

In contrast, the crystalline transition-metal complexes of diimine synthesized by *Sellmann et al.*[3] are sufficiently stable for X-ray diffraction analysis. Structural analysis of the complex $N_2H_2[Cr(CO)_5]_2$ *(1)* was undertaken to provide definite structural parameters of diimine, which presumably is also of biological importance.

Diiminebis(pentacarbonylchromium) *(1)* crystallizes from tetrahydrofuran (THF) solution as dark red needles[4], which rapidly transform into shiny—X-ray amorphous—needles of *(1)* on reduction of the THF partial pressure. According to structural analysis, the red needles obtained initially are crystals of the solvated complex $N_2H_2[Cr(CO_5)]_2 \cdot 2THF$ *(2)*; they can be stored for several weeks in a nitrogen atmosphere at −50 °C under THF vapor pressure.

The addition compound *(2)* crystallizes in the triclinic space group P$\bar{1}$ with $a = 1903$, $b = 1027$, $c = 637$ pm; $\alpha = 97.3$, $\beta = 97.9$, $\gamma = 95.9°$; $Z = 2$; d_{calc} 1.528 g cm^{-3} (1310 measured diffraction intensities, agreement factor $R_1 = 0.068$).

In agreement with the results of earlier investigations by *Sellmann et al.*[3], compound *(2)* contains two pentacarbonyl units bridged by a diimine ligand. The molecule has a crystallographically determined center of inversion in the middle of the N=N bond. The diimine ligand therefore has *trans*-configuration[5].

Each of the hydrogen atoms of the diimine ligand forms a bridge bond to the oxygen atom of a THF solvate molecule.

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[**] This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Leibniz-Rechenzentrum der Bayerischen Akademie der Wissenschaften.

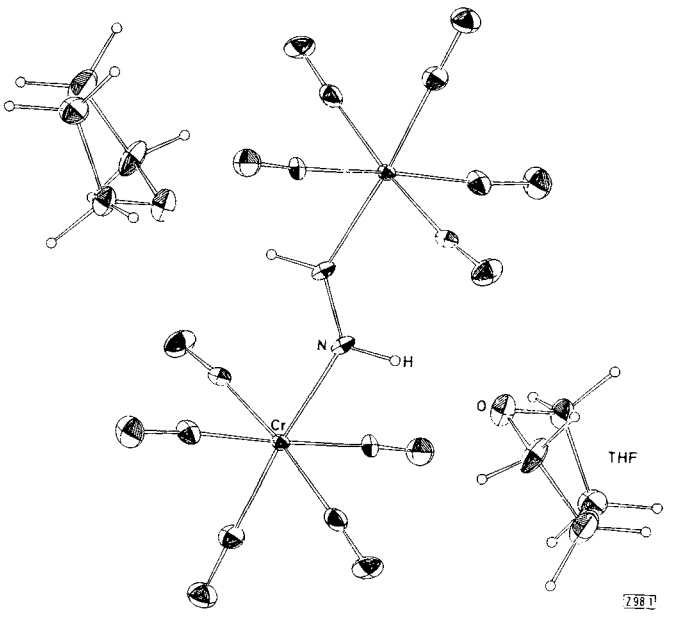


Fig. 1. Structure of the diimine complex $N_2H_2[Cr(CO)_5]_2 \cdot 2THF$ *(2)*.

The $N-O_{THF}$ distances, with a value of 290±1 pm, are in the range typical for N—H—O bridge bonds. The angles N—N—O_{THF} and N—N—Cr are 122.3 and 130.5° respectively. The N=N distance, with a value of 125 pm, corresponds in length to that of a N=N double bond observed for organic azo compounds[6].

The chromium atoms have an almost octahedral surrounding. The $Cr-C_{CO}$ distances have a mean value of 190 pm; the carbonyl groups *trans* to the nitrogen atoms of the diimine appear to be somewhat more tightly bound ($Cr-C_{CO}$ 186 pm). The $Cr-N_{sp^2}$ distance is 207.6±1 pm; it is considerably shorter than the $Cr-N_{sp^3}$ distance in tricarbonyldiethylenetriaminochromium (218.5 pm)[7]; this may be indicative of a small amount of π bonding in the Cr—N bond[8]. The amount of π bonding must be small, since otherwise lengthening of the N=N distance would be expected, such as is observed in dimeric nitroso compounds (*trans*-$(O_2NCH_2CH_2NO)_2$, $d_{N\,N} = 130.4$ pm[9]; *cis*-$(C_6H_5NO)_2$, $d_{N\,N} = 132.3$ pm[10]).

The structure analysis of *(2)* constitutes the first X-ray crystallographic evidence for the existence of diimine[11]. Diimine is present in the solvated complex *(2)* in the *trans* form. The extraordinarily labile free HN=NH is stabilized in *(2)* as a bridge ligand between two $Cr(CO)_5$ units.

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CAS Registry Number: *(1)*, 53318-34-6

[1] *N. Wiberg*, *H. Bachhuber*, and *G. Fischer*, Angew. Chem. *84*, 889 (1972); Angew. Chem. internat. Edit. *11*, 829 (1972).

[2] *N. Wiberg*, *G. Fischer*, and *H. Bachhuber*, Chem. Ber. *107*, 1456 (1974).

[3] a) *D. Sellmann*, J. Organometal. Chem. *44*, C46 (1972); *D. Sellmann*, *A. Brandl*, and *R. Endell*, *ibid. 49*, C22 (1973); Angew. Chem. *85*, 1121 (1973); Angew. Chem. internat. Edit. *12*, 1019 (1973); b) *ibid. 85*, 1122 (1973), and *12*, 1019 (1973), respectively.

[4] We thank Dipl.-Chem. *A. Brandl* for preparing samples of the crystals.

[5] According to IR spectroscopic investigations [3b], the N_2H_2 ligand in the unsolvated complex *(1)* has a symmetry deviating from the *trans* configuration.

[6] A much shorter N=N distance has been observed in bis(trimethylsilyl)diimine: *M. Veith* and *H. Bärnighausen*, Acta Crystallogr., in press.

[7] *F. A. Cotton* and *D. C. Richardson*, Inorg. Chem. *5*, 1851 (1966).

[8] The chromium-nitrogen distance in *cis*-Cr(diene)CO_4 [6] is possibly changed compared to a normal $Cr-N_{sp^2}$ distance by strains in the chelate

system: *F. A. Cotton* and *M. D. LaPrade*, J. Amer. Chem. Soc. *91*, 7000 (1969).

[9] *F. B. Boer* and *J. W. Turley*, J. Amer. Chem. Soc. *91*, 1371 (1969).

[10] *D. A. Dietrich, I. C. Paul*, and *D. Y. Curtin*, Chem. Commun. *1970*, 1710.

[11] In the case of the complexes $[(R_2PC_2H_4PR_2)_2MX_2]N_2H_2$ with R = alkyl, aryl; X = halogen; and M = Mo, W, described by *Chatt et al.*, only the presence of a hydrazido ligand (=N · NH_2) has so far been detected: *G. A. Heath, R. Mason*, and *K. M. Thomas*, J. Amer. Chem. Soc. *96*, 259 (1974).

Anionic Structure of the So-called Ammonium Dimolybdate $(NH_4)_2Mo_2O_7$

By *Imme Knöpnadel, Hans Hartl, Wolf-Dietrich Hunnius*, and *Joachim Fuchs*[*]

$(NH_4)_2Mo_2O_7$ crystallizes as colorless platelets from a warm concentrated solution (60 °C) of ammonium heptamolybdate, $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, to which ammonia and ammonium chloride have been added[1].

The triclinic unit cell of space group $P\bar{1}$ contains two formula units. Its lattice constants are: $a = 7.261 \pm 0.001$, $b = 7.961 \pm 0.001$, $c = 7.326 \pm 0.001$ Å; $\alpha = 82.63 \pm 0.05$, $\beta = 94.47 \pm 0.05$, $\gamma = 114.64 \pm 0.05°$.

The structure was elucidated on the basis of three-dimensional diffraction data with evaluation of 3607 independent reflections and refinement to an R value of 5.4 %.

The salt does not contain a dimeric, but rather a *polymeric* anion, in which the MoO_6 octahedra and MoO_4 tetrahedra are linked to form chains (Fig. 1). The coupling is of a completely different type from that in $Na_2Mo_2O_7$ prepared from melts, which likewise contains tetrahedral and octahedral building units[2].

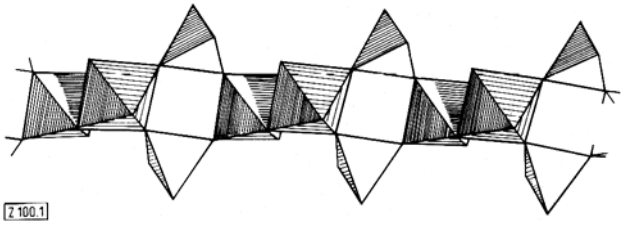


Fig. 1. Anionic structure of $(NH_4)_2Mo_2O_7$.

Two MoO_6 octahedra are bound *via* a common edge [oxygen atoms O^6 and $O^{6'}$; cf. Fig. 2] across a symmetry center to give a Mo_2O_{10} unit. Each of the Mo_2O_{10} units are linked stepwise by two MoO_4 tetrahedra *via* common oxygen atoms [O^3 and O^7] to give infinite chains. The distances between the molybdenum atoms are 3.158 [Mo^1—Mo^2] and 3.169 Å [Mo^2—$Mo^{2'}$]. The molybdenum-oxygen distances are shown in Fig. 2. The anion chains are crosslinked *via* a system of hydrogen bonds through ammonium ions. The distances between the nitrogen atoms and their nearest neighboring oxygen atoms are 2.79 to 2.99 Å.

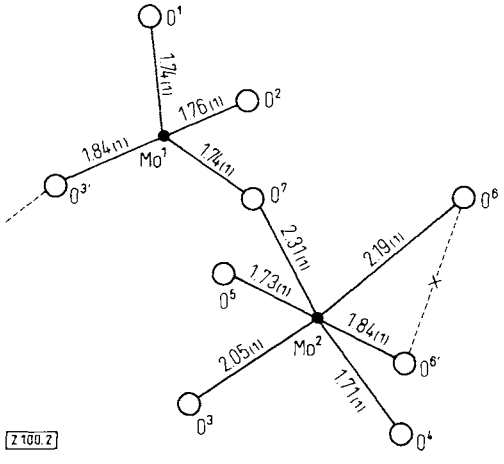


Fig. 2. Molybdenum-oxygen distances [Å] in $(Mo_2O_7^{2-})_\infty$; standard deviations in units of the last decimal place are given in parentheses.

The compound is conveniently named according to the "base-acid ratio", $(NH_4)_2O{:}MoO_3 = 1{:}2$, as ammonium (1:2)-molybdate. Knowledge of its structure is of interest for understanding the formation of polyanions in aqueous solution.

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[1] *W.-D. Hunnius*, Z. Naturforsch., in press.

[2] *I. Lindqvist*, Acta Chem. Scand. *4*, 1066 (1950); *M. Seleborg*, Acta Chem. Scand. *21*, 499 (1967).

ABSTRACTS

Reviews

Abstracts of selected progress reports and review articles

The characterization of chain molecules by their dipole moments is the subject of a review by *J. E. Mark*. Theoretical analysis of the measured dipole moments of randomly coiled chain molecules can provide valuable information on the conformational energies and spatial configurations of such molecules. Examples are "stereochemical copolymers", *e.g.* polyvinyl chloride and poly(*p*-chlorostyrene) and "chemical copolymers", *e.g.* poly(*p*-chlorostyrene-*p*-methylstyrene) copolymer. [The Use of Dipole Moments to Characterize Configurations of Chain Molecules. Accounts Chem. Res. *7*, 218—225 (1974); 63 references]

[Rd 730 IE—L]

The biosynthesis of collagen is described by *E. J. Miller* and *V. J. Matukas*. Five genetically different α-chains of collagen are known which aggregate to give four types of trimers. The distribution of the aggregate types is in part organ-specific. The messenger RNA for the synthesis of the α-chains stems from one cistron; the hydroxylation of prolyl and lysyl residues takes place simultaneously or immediately after the translation. The chains aggregate and form helices as they are still growing on the polysomes, while glycosylation to procollagen takes place later. Procollagen is finally converted by proteolysis into collagen. The findings are discussed in connection with the concepts of cell morphology, localization, transport and

secretion of collagen. [Biosynthesis of Collagen. Fed. Proc. *33*, 1197—1204 (1974); 97 references]

[Rd 735 IE—R]

The azide method for peptide bond synthesis introduced by *Curtius* is still an important coupling method, since the starting compounds are readily accessible, little racemization takes place, and long peptide fragments can be synthesized with minimal protection of amino acid side chains. A review by *Y. S. Klausner* and *M. Bodansky* starts with a description of hydrazide and azide formation and a discussion of the side reactions occurring in such formations and in coupling processes (*e.g.* in the Curtius rearrangement, azide→isocyanate). Modifications of the azide method, especially those which should repress amide formation during preparation of the azides, are exemplified by preparative methods (Honzl-Rudinger and Medzihradszky method). The formation of small amounts of dispiro isomers in the azide coupling cannot be completely ruled out, but is much less likely than, *e.g.* in the case of the dicyclohexylcarbodiimide method. The article deals with the use of the azide method in the solid phase synthesis of peptides, the cyclization of peptides, and the polymerization of peptide azides. The use of cyclocarbodiimides for the synthesis of peptides is briefly touched on. [The Azide Method in Peptide Synthesis. Its Scope and Limitations. Synthesis *1974*, 549—559; 153 references]

[Rd 738 IE—M]

ESR spectra of binuclear transition metal complexes are the subject of a review by *T. D. Smith* and *J. R. Pilbrow*. The theory of magnetic interaction between pairs of similar and dissimilar ions of spin 1/2 is treated extensively. A compilation of interpreted ESR spectra of binuclear complexes with the central ions Cu^{2+}, VO^{2+}, and Ti^{3+} follows. Some denaturization products of naturally occurring Cu^{2+} compounds are also considered. [The Determination of Structural Properties of Dimeric Transition Metal Ion Complexes from EPR Spectra. Coord. Chem. Rev. *13*, 173—278 (1974); 186 references]

[Rd 741 IE—H]

Recent results in the search for trace elements in nutrition are discussed in an article by *K. Schwarz*. Such investigations necessitate very effective isolating systems and feeding of animals with highly pure substances. The severe damages caused by selenium deficiency have been known for a long time. In the meantime it has also been established that this element is present in higher organisms in glutathione peroxidase and in a special cytochrome. The organism requires very small trace amounts of tin and vanadium; the exact biochemical function of these two elements, however, is still unknown. The same applies to fluorine, which appears to have other, more general biochemical effects in addition to being an effective anticaries agent. Silicon, one of the most abundant elements in the earth's crust, is necessary for bone formation and growth of connective tissue. A review is given of other elements which could play a role as trace elements in organisms. [Recent Dietary Trace Element Research, Exemplified by Tin, Fluorine, and Silicon. Fed. Proc. *33*, 1748—1757 (1974); 53 references]

[Rd 742 IE—R]

Silicon as trace element in organisms is reviewed by *E. M. Carlisle*. Lack of this element in higher animals leads to general irregularities in growth. In calcification of young bones, calcium interacts with silicon; silicon is also found in articular cartilage and connective tissue, where it probably plays a role in the crosslinking of protein-mucopolysaccharide complexes. It is also assumed to participate in the biosynthesis of mucopolysaccharides. Many tissues are more silicon-deficient in older individuals than in younger ones. [Silicon as an Essential Element. Fed. Proc. *33*, 1758—1766 (1974); 66 references]

[Rd 743 IE—R]

Vanadium as an essential nutrient is the title of a review authored by *L. L. Hopkins* and *H. E. Mohr*. Animals fed on a vanadium-free diet remain stunted—bodily development and growth of hair and feathers are retarded. The growth of teeth, bone formation, reproduction, and the survival rate of young animals are also adversely affected. Moreover, erythrocyte formation and iron metabolism are far from normal. Studies on the nutritional requirement would suggest that normal food does not contain more vanadium than is absolutely necessary, but rather that there is a general deficiency of this essential element. [Vanadium as an Essential Nutrient. Fed. Proc. *33*, 1733—1775 (1974); 14 references]

[Rd 745 IE—R]

BOOK REVIEWS

Carbon-13 NMR Spectroscopy. By *J. B. Stothers*. Organic Chemistry—A Series of Monographs, Vol. 24. Academic Press, New York—London 1972. 1st edit., xi, 559 pp., Numerous tables, bound $ 24.—.

The present monograph represents a summary of almost all the papers on ^{13}C-NMR spectroscopy published to the end of 1970. Following a short introduction on the theory (Chapter 1) and methods (Chapter 2) of NMR spectroscopy, Part II (Chapters 3—8) describes the ^{13}C-chemical shifts of hydrocarbons and their substituted derivatives, organometallic compounds and carbenium ions, heterocyclics, carbonyl compounds, and nitriles. Part III is devoted to ^{13}C coupling constants. A general introduction to the theory of ^{13}C coupling in Chapter 9 is followed by detailed treatment of the ^{13}C-^{1}H coupling constants in Chapter 10 and a review of the ^{13}C-^{19}F and ^{13}C-^{13}C coupling constants and other heteronuclear couplings. Applications of ^{13}C resonance to the solution of structural or stereochemical problems in organic compounds, polymers, and natural products are briefly dealt with in Part IV (Chapter 11). Examples of the elucidation of reaction mechanisms and biosynthetic pathways by ^{13}C resonance and a brief treatment of solvent effects complete the work.

The monograph is well arranged and intelligibly written. Its perusal will present no great difficulty even to the beginner in NMR. The ^{13}C chemical shifts are uniformly converted or given against tetramethylsilane as standard, which greatly facilitates comparison with recent measurements. It is true that new routine methods in ^{13}C resonance, *e.g.* pulse Fourier transform spectroscopy, are but briefly alluded to, although the significance of such methods for ^{13}C resonance was recognized already in 1970. In relation to the scope of the book, and compared to other NMR monographs, the illustrations are also somewhat scanty. The provision of comprehensive author and subject indices, as well as of an index of compounds whose ^{13}C parameters are discussed, tabulated, or illustrated in the figures, will greatly facilitate the reader's

task. For this reason the monograph, composed by one of the pioneers of ^{13}C resonance, is not only a comprehensive reference work (at least until 1970) but, by virtue of its clear arrangement, a pleasure to use. It will thus be a valuable aid to all concerned with or interested in NMR spectroscopy.

Eberhard Breitmaier [NB 220 IE]

Electrochemistry of Cleaner Environments. Edited by *J. O'M. Bockris*. Plenum Press, New York—London 1972. 1st Edit., xiii, 296 pp., numerous figures, bound $ 26.—.

It is well known that protection of the environment is a problem of growing concern to our modern industrial society. What is probably less well known is that it has been recognized for some years that a solution to practically all these problems is to be expected primarily from electrochemistry. The present book is thus very topical, and its readership should extend far beyond the narrow field of electrochemistry.

The replacement of combustion-engined cars by electric cars is unthinkable without electrochemical fuel cells or accumulators. Development is being concentrated on accumulators at present. The contribution by *E. H. Hietbrink et al.* presents a concise survey of this development, covering all the most important points in full. It is not yet certain which of the battery systems, *e.g.* the Pb/PbO_2, Zn/MnO_2, Fe/air, Li/chlorine, or Na/sulfur battery, will one day become the current source of choice for electric cars. One thing that is certain, however, is that the production of electrical energy is not itself a limiting factor.

The electrochemical treatment of effluents *(A. T. Kuhn)*, whether by electrolysis, electroflotation, or electrodialysis, and the electrofiltration of gases *(E. C. Potter)* are methods that have been in industrial use for a long time and that will certainly become more important in the future.

The contribution by *T. A. Henrie* and *R. E. Lindstrom* points out the possibility of digesting sulfide ores by treatment with electrolytically produced hypochlorous acid. Instead of SO_2, which pollutes the atmosphere, this yields an aqueous solution of the corresponding metal sulfate, which can be refined directly by electrolysis. Electrochemistry also provides many methods for continuous trace analysis (CO, SO_2, NO_x, *etc.*), which are discussed by *B. D. Epstein*.

R. P. Hammond and *D. P. Gregory et al.*, in their very detailed, forward-looking contributions, finally examine how the rapidly growing demand for electrical energy can be met and distributed. It is thought that the former can be achieved by fission or fusion power stations of the order of 10000 MW, floating on artificial islands in the ocean. For distances greater than 800 km, the transport of hydrogen, produced on the spot by electrolysis of water, is found to be more economical than the conduction of current. The pipe system filled with hydrogen also serves as a welcome energy store for use as a buffer. In the case of this "hydrogen economy", the consumer burns the hydrogen to produce heat without harmful exhaust gases, while part of it is used to produce current in fuel cells. A superabundance of electrical energy in the future would also lead to an immense resurgence of electrochemistry, *i.e.* the electrosynthesis of inorganic and organic compounds. This point is unfortunately not discussed in the book, an omission that is all the more surprising in view of the space devoted to relatively obscure topics such as the increase in the CO_2 content of the atmosphere (a brilliantly written contribution by *G. N. Plass*). Several references are made to the extensive use of hydrazine as a fuel in fuel cells, though in all probability, even after the production costs have been reduced, this fuel will be banned because of its toxicity (max. permissible conc. = 0.1 ppm). The metal-selective electrolytic processing of whole scrapped cars, which the editor seriously discussed in his introduction, is another idea that will probably never be realized.

These minor faults and imbalances in the distribution of topics in no way detract from the solid overall impression made by this work. It can be recommended to electrochemists and environmental specialists, and also to all those who are interested in learning about forward-looking technical problems.

Fritz Beck [NB 228 IE]

Comprehensive Biochemistry. Edited by *M. Florkin* and *E. H. Stotz*. Vol. 30. A History of Biochemistry. Part I: Proto-Biochemistry; Part II: From Proto-Biochemistry to Biochemistry. Elsevier Publishing Company, Amsterdam—London—New York 1972. 1st Edit., xvii, 343 pp., 64 figs., 4 tables, bound $ 25.00.

As a reward, so to speak, after 29 volumes of exact biochemistry[*] (not yet published in full), this volume reads like a novel. The shrewd, globe-trotting, broadly educated, and independently thinking editor *Florkin* has taken it upon himself to write the history of biochemistry. Apart from his international personal connections, his own historical studies qualify him to deal with the history of medicine at the crossroads of European intellectual history, the Belgian contact zone of many traditions since the middle ages. Here he presents the first part of a history of development that shows how the relationships between the philosophical concepts of the observation of nature and the empirically reproducible physical laws interacted and molded one another from the pre-Socratics up to the vitalists, and how inductive research finally overcame the dominance of *a-priori*, often esthetically motivated thought patterns and developed from *Occam*'s razor to the scalpel of cell biology. However, the scientist, now freed from the constraints of prejudice, readily falls once again into new fetters of authority, and the chapters in which *Florkin* deals with the cellular concept and *Liebig*'s theories of metabolism are particularly interesting and stimulating. This is especially true for the partisan-minded reader, who is provided here with a detached overview. Outstandingly descriptive and critically argumentative, the book is one of the most worthwhile and most generally instructive that could be found in a scientific library. The author never yields to the cheap temptation to present unconventional views without foundation, or to provoke by iconoclasm or *vice versa*.

One thus obtains new and reflectively inclining insights into the relationships of the history of thought and the relativity of our historical views. It is merely mentioned in passing that the presentation of the book is also excellent. Thus it is with great suspense, hopefully soon to be relieved, that we await the two further volumes, which will set the keystone that holds the arch of biochemistry together.

L. Jaenicke [NB 230 IE]

Kunststoff-Handbuch. Band 8. Polyester (Plastics Handbook, Vol. 8. Polyesters). Edited by *R. Vieweg* and *L. Goerden*. Carl Hanser Verlag, München 1973. 1st Edit., xxvii, 775 pp., 498 figs., 152 tables, bound DM 275.—.

The present volume deals with three important plastics, *i.e.* polycarbonates, polyalkylene terephthalates, and unsaturated polyesters (UP resins), of which the first and last might well have merited a special volume each. Nevertheless, it is justifiable to combine them in a single volume, since the polymers in these three plastics are all built up *via* ester groups. On the other hand the UP resins, as thermosets, have entirely

[*] Cf. Angew. Chem. internat. Edit. *10*, 361 (1971).

different processing characteristics and applications from the thermoplastic polycarbonates and polyalkylene terephthalates.

The basic division of the earlier volumes[*] into constitution, preparation, structure and properties, and processing and use is retained for these three plastics. Special sections on cutting agents, accelerators, inhibitors, glass-fiber reinforcement, and fillers are added in the case of the UP resins, corresponding to their different processing. It would have been interesting to learn more about the use of polycarbonates and UP resins, *e.g.* in the USA. The reason why the section on polyalkylene terephthalates is rather short is probably that this plastic was still in the development stage during the preparation of this volume. One should expect more in a new edition.

It is pleasing to note that a relatively large amount of space has been given to processing and use in the case of the polycarbonates, though the scientific side has not been neglected as a consequence. This is also true of the UP resins, but the sections on aids and fillers, glass fibers, *etc.* are also very informative.

The editors have managed to obtain the services of an outstanding specialist for each chapter, and the volume can therefore be regarded as very successful. Access to the original literature and to patents is facilitated by the extensive bibliography following each chapter. The volume will prove to be a good, fast source of instruction for processers, engineers, architects, and electrical engineers, as well as for chemists and physicists, and can be warmly recommended.

Otto Horn [NB 231 IE]

Die räumliche Struktur organischer Moleküle (The Steric Structure of Organic Molecules). By *Charles C. Price*. "taschentext" Vol. 10. Verlag Chemie, GmbH—Physik-Verlag, Weinheim 1973. 1st Edit., x, 102 pp., 38 figs., 18 tables, bound DM 12.80.

The aim of the "taschentext" series for chemistry and biology students, "to find means for the more effective presentation of fields, in which several disciplines are involved", and the purpose of this book, to familiarize these students with the fundamental factors that determine the principal properties of materials made from natural or synthetic polymers, are very commendable.

However, the title (original edition: Geometry of Molecules, 1971) may mislead the beginner into thinking that the whole of organic stereochemistry is dealt with here. The different use of the term "structure" in this connection can be seen from a comparison of the contents with those of books having related titles, *e.g. Coulson* (The Shape and Structure of Molecules), *Barrett* (Die Struktur der Atome und Moleküle [The Structure of Atoms and Molecules]), *Barry/Barry* (Die Struktur biologisch wichtiger Moleküle [The Structure of Biologically Important Molecules]), *Allinger/Allinger* (Strukturen organischer Moleküle [Structures of Organic Molecules]).

The material is divided in a logical manner into five chapters: The Geometry of Small Molecules (19 pp.); Intermolecular Forces (9 pp.); Dynamic Aspects of Molecular Geometry (23 pp.); Properties of Polymers (26 pp.); and Properties of Biopolymers (15 pp.).

The number of printing errors (pp. 15, 45, 55; 46, 52, 53, 84) is within normal limits. More objectionable are a number of weak points that could have been avoided: A pair of electrons, for example, spends "more time" in the neighborhood of the chlorine atom (p. 14). The title of the section "Asymmetric (Chiral) Molecules", which is too short (1 1/2 pp.) and also tedious (compare the lively chapter "Molecular Dissymmetry" in *Barry/Barry*, see above), is didactically by no means the best, nor are the unusual arrangement of the lactic acid formulas (p. 17) and the representation of inversion at the amine nitrogen (p. 18). The name Perlon should at least be mentioned in the discussion of 6,6-nylon (p. 69). The designation *trans* should not be applied to single bonds (p. 52). A note about the non-drop-like shape of p-orbitals would have been useful on p. 15. In the drawings of molecular models (pp. 16, 17), the bonds lying in the same plane should have been drawn as lines of equal thickness; the striped bonds are disturbing. The word "gefaltet" (folded) should have been used instead of "gebuckelt" (buckled) (cyclopentane ring, p. 45). On p. 47, orbital and molecular models are twisted in relation to each other, though they are placed together for comparison. On the same page there are formulas and corresponding projections that are rather disordered in space.

However, these weaknesses in a few details are more than outweighed by the convincing explanations in the text, which arouse understanding of and above all interest in the "giant molecules".

On the whole, the book fills a gap. The combination of elementary stereochemistry, polymer chemistry, and biochemistry in such a small space may be regarded as successful. This introduction can be recommended not only to those addressed in the foreword, but also to those who are fully trained in neighboring disciplines. *Fritz Vögtle* [NB 232 IE]

Elektrotauchlackierung (Electropainting). By *W. Machu*. Verlag Chemie GmbH, Weinheim 1974. 1st Edit., x, 338 pp., 133 figures, 32 tables, bound DM 98.—.

It has not taken many years for electropainting to find wide application as an economic process. Numerous publications have appeared during this time, dealing with the development of coating materials and the latest situation regarding plant and engineering. In the present book *W. Machu* has evaluated a considerable part of this literature and worked it up into a comprehensive review of this modern technique. He deals here with the physical and chemical principles of anodic deposition of paint, the importance of voltage and current strength, the throwing power, pretreatment of the metal, the composition and testing of the varnish materials, special fields of application, plant and procedures, and economic considerations. In conclusion, there is an extensive review of patents. Thus, the book is of equal interest to users and to manufacturers of paints and plants.

The mechanism of film formation by means of electropainting and the influence of the various paint and deposition parameters on the resulting coating are not yet fully understood. The section of the book dealing with this subject adds nothing to existing knowledge: the sometimes inadmissible generalizations of experimental results on specialized varnish systems that are found in the literature cited are here reported without discussion.

The chapters about pretreatment of the metal before electrodeposition varnishing are very detailed. The author's extensive experience with metal cleaning and phosphatizing makes this part of the book a valuable source of information for both users and paint manufacturers. It is disturbing that the pretreatment process of only one supplier is cited. The chapters about paint formulation and supervision of the immersion bath are brief, and are necessarily incomplete for a process whose further development is still under active study.

The descriptions of plant and procedure in electropainting with their numerous illustrations and examples of application, provide a good review of possible applications of the process. Many technical details of the plants are of interest to

[*] Cf. Angew. Chem. internat. Edit. *11*, 947 (1972).

the user. Perhaps some of the misprints, which sometimes distort the sense, could be avoided in a new edition of the book.

Dietrich Saatweber [NB 233 IE]

Spurenelemente in Wein und anderen Getränken (Trace Elements in Wine and Other Beverages). By *H. Eschnauer*. Verlag Chemie GmbH, Weinheim 1974. 1st Edit., viii, 220 pp., 7 figures, 129 tables, bound DM 78.—.

In this book information concerning the trace elements of wine and other beverages is presented fully systematically and for the first time. The first part of the book deals with the general problems of trace analysis, namely separation processes, methods of determination, and the reliability of the results, together with the development of the analysis of wine. Particular attention is paid to modern analytical procedures which first made trace element analysis possible.

This is followed by presentation of the actual results, arranged according to the elements. In each case the most important properties of the elements are mentioned and these are followed by their contents in alcoholic beverages, their raw materials, and their intermediate products. Here the distinction between primary and secondary components deserves close attention. Fundamental relationships between these components and, *inter alia*, the soil properties, climatic conditions, and ecological processes are described. A survey of the most common and the most recommended analytical methods is included. Each chapter is supplemented by an extensive bibliography.

A summary of the mineral and trace element content of alcoholic beverages and of German mineral waters is provided in the last section. Nutritional, biological, biochemical, fermentational, and plant-physiological aspects are discussed.

This book deserves special mention because of the wealth of material collected, the clear arrangement of the text, the comprehensive, in part tabular, presentation, and not least the large number of references. As a reference work it constitutes a valuable tool for all the specialists concerned.

W. Thieme [NB 234 IE]

Polymer Spectroscopy. Edited by *D. O. Hummel*. Verlag Chemie GmbH, Weinheim 1974. 1st Edit., xii, 401 pp., 262 figures, 76 tables, bound DM 125.—.

This monograph contains a review of the present state of the theory and applications of vibration spectroscopy (IR, Raman), magnetic resonance (NMR, ESR) and mass spectroscopy of synthetic polymers. Several other extremely important spectroscopic methods, such as UV, X-ray structure analysis, and neutron diffraction, have purposely been omitted, and the same applies to discussion of biopolymers.

In the first section of Chapter 2, *H. Tadokoro* and *M. Kobayashi* undertake the difficult task of presenting, briefly and with special reference to polymers, the procedure in the analysis of an IR spectrum and the theoretical prediction of vibrational frequencies by group-theory treatment of the problem. The application of the procedure described is demonstrated on selected polymers.

In Section 2 of Chapter 2, by *D. O. Hummel*, the polymer spectroscopist who is not so familiar with this very complicated subject will find the empirical method of IR spectroscopy of polymers described for many examples.

P. J. Hendra records very clearly, in Section 3 of Chapter 2, the methods, scope, and examples of Raman spectroscopy of polymers now that lasers are used as radiation sources.

Chapter 3, by *E. Klesper* and *G. Sielaff*, has as its main theme the statistics of chain-polymerization of synthetic homo- and copolymers, with NMR spectroscopy providing the analytical method. For a few examples the systematic analytical procedure for NMR spectra and comparison of the theoretical-statistical with the experimental results are demonstrated in full detail. Unfortunately, the possible introduction of ^{13}C-NMR spectroscopy is rarely taken into account. A detailed collection of references to all the synthetic polymers examined by NMR spectroscopy up to 1972 closes this chapter.

In Chapter 4, *H. Fischer* and *D. O. Hummel* introduce ESR Spectroscopy, and not exclusively for polymers. The examples treated give a very good survey of the ESR spectra of polymer radicals that are formed by irradiation, on radical polymerization or on mechanical treatment.

D. O. Hummel, H.-D. Schlüddemage, and *K. Rübenacker* describe in Chapter 5 the limited possibilities for mass spectrometry in the field of high polymers, with a good selection of examples.

With its many thoroughly treated examples, this book will provide a very good insight into this material and a great many valuable suggestions to the polymer chemist interested in empirical spectroscopy; for the theoretically oriented polymer chemist, the necessarily very brief and in part highly specialized theoretical treatments will hardly suffice, although the extensive bibliography will be of great help in further study of the subject. Some hints for chemists interested in biopolymers would have been welcome.

Horst Friebolin [NB 235 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal.

Ullmanns Encyklopädie der technischen Chemie. Edited by *E. Bartholomé, E. Biekert, H. Hellmann*, and *H. Ley* †. Vol. 8: Antimon und Antimon-Verbindungen bis Brot und andere Backwaren. Verlag Chemie, Weinheim 1974. 4., newly revised edition. xv, 730 pp., bound, DM 385.—.

Die Chemie der Pyrrole. By *A. Gossauer*. Vol. 15 of the series "Organische Chemie in Einzeldarstellungen". Edited by *H. Bredereck, K. Hafner*, and *E. Müller*. Springer-Verlag, Berlin 1974. xx, 433 pp., bound, DM 158.—.

Saturated Heterocyclic Chemistry, Vol. 2. Senior Reporter: *W. Parker*. The Chemical Society, London 1974. x, 407 pp., bound, £ 13.50.—A volume from the series "Specialist Periodical Reports".

Organometallic Chemistry of Titanium, Zirconium, and Hafnium. By *P. C. Wailes, R. S. P. Coutts*, and *H. Weigold*. From the series "Organometallic Chemistry". Academic Press, New York 1974. vii, 302 pp., bound, $ 29.50.

Mechanical Properties of Polymers and Composites, Vol. 1. By *L. E. Nielsen*. Marcel Dekker, Inc., New York 1974. xiv, 255 pp., bound, £ 13.50.

Enzymkinetik. A programmed introduction to the theory of enzyme kinetics and its practical application. By *J. Ahler, A. Arnold, Fr. R. von Döhren*, and *H. W. Peter*. Gustav Fischer Verlag, Stuttgart 1974. IX, 188 pp., stitched, DM 24.—.

1. Korrosionum. Die Bedeutung der Korrosion für Planung, Bau und Betrieb von Anlagen der chemischen und petrochemischen Technik sowie in der Mineralölindustrie. Erfahrungsaustausch für Praktiker. Arranged by DECHEMA (Deutsche Gesellschaft für chemisches Apparatewesen). Edited by *H. Gräfen*, *F. Kahl*, and *A. Rahmel*. Verlag Chemie, Weinheim 1974. 407 pp., bound, DM 68.—.

Lehrbuch der Lebensmittelchemie. By *J. Schormüller*. Springer-Verlag, Berlin 1974. 2., completely revised edition, xvi, 832 pp., bound, DM 98.—.

Molecular Spectroscopy, Vol. 2. Senior Reporters: *R. F. Barrow*, *D. A. Long*, and *D. J. Millen*. The Chemical Society, London 1974. XII, 579 pp., bound, £ 18.00.—A volume in the series "Specialist Periodical Reports".

Air Pollution, Part B — Prevention and Control. By *J. O. Ledbetter*. Marcel Dekker, Inc., New York 1974. XIII, 286 pp., stitched, $ 11.75.

Aromatic and Heteroaromatic Chemistry, Vol. 2. Senior Reporters: *C. W. Bird* and *G. W. H. Cheeseman*. The Chemical Society, London 1974. XVI, 519 pp., bound, £ 16.00.—A volume in the series "Specialist Periodical Reports".

Modern Quantitative Analysis: Experiments for Non-Chemistry Majors. By *G. G. Guibault*. Marcel Dekker, Inc., New York 1974. V, 241 pp., stitched, $ 7.75.

Biochemische Genetik. By *R. A. Woods*. Gustav Fischer Verlag, Stuttgart 1974. VI, 94 pp., stitched, DM 8.80.

Funktionen biologischer Membranen. Einführung in den zellulären Stofftransport. By *M. Davies*. Gustav Fischer Verlag, Stuttgart 1974. VI, 94 pp., stitched DM 8.80.

Zelldifferenzierung. By *J. M. Ashworth*. Gustav Fischer Verlag, Stuttgart 1974. VI, 95 pp., stitched, DM 8.80.

Zellentwicklung. Zelluläre Interaktionen in der Embryonalentwicklung. By *D. R. Garrod*. Gustav Fischer Verlag, Stuttgart 1974. VI, 95 pp., stitched, DM 8.80.

Introduction to Particle Production in Hadron Physics. By *S. Humble*. Academic Press, London 1974. VIII, 253 pp., bound, £ 6.80/$ 17.50.

Advances in Magnetic Resonance, Vol. 7. By *J. S. Waugh*. Academic Press, London 1974. VIII, 322 pp., bound, £ 13.70.

Organotransition Metal Chemistry. A Mechanistic Approach. By *R. F. Heck*. Academic Press, London 1974. XII, 338 pp., bound, £ 12.95.

Arzneimittelallergie. Grundlagen und Klinik. XII. Congress of the German Society for Allergy and Immunity Research in Wiesbaden, 14.—15. April 1972. Supplementband I der Zeitschrift für Immunitätsforschung. Edited by *M. Werner* and *W. Gronemeyer*. Gustav Fischer Verlag, Stuttgart 1974. XIV, 307 pp., stitched, DM 128.—.

Biochemical Reactors. By *B. Atkinson*. Pion Limited, London 1974. IX, 267 pp., bound, £ 5.00.

Solid State Reactions. By *H. Schmalzried*. Verlag Chemie, Weinheim and Academic Press, Inc., London 1974. X, 214 pp., bound DM 54.—.

Arzneimittelprüfung—Arzneimittelrecht. Nationale und internationale Bestimmungen und Empfehlungen. By *H. Hasskarl* and *H. Kleinsorge*. Gustav Fischer Verlag, Stuttgart 1974. VIII, 229 pp., stitched, DM 48.—.

Korrosion und Korrosionsschutz. By *H. Orth*. Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart 1974. X, 278 pp., stitched, DM 16.—.

Physikalische Chemie. Eine Einführung für Ingenieure. By *L. Riedel*. Bibliographisches Institut, Mannheim 1974. XV, 406 pp., stitched, DM 38.—.

Stereochemie und Reaktivität organischer Verbindungen. Eine Einführung. By *W. Kraus*. Vol. 5 of "Studienbücher Naturwissenschaft und Technik". Bertelsmann Universitätsverlag, Düsseldorf. 150 pp., stiched DM 24.—.

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